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EXPERIMENTAL PERICARDITIS: THE PATHOLOGIC PHYSIOLOGY OF CONSTRICTIVE PERICARDITIS*

JAMES P. ISAACS, B. NOLAND CARTER II AND J. ALEX HALLER, JR.

Received for publication November 28, 1951

The purpose of this study was to investigate the pathologic physiology of constrictive pericarditis, as an aid both to the diagnosis and treatment of this disease.

To accomplish this purpose it was necessary to develop a method for the production of experimental pericarditis in dogs. It was also necessary to obtain hemodynamic data from these dogs by cardiac catheterization before and after chronic pericardial constriction and after removal of the constricting pericardial scar.

Non-localized experimental pericardial constrictions have been produced (1, 2, 3, 4, 5, 6, 7, 8, 9, 10) employing many different fibroplastic agents including Dakin's solution, asbestos, aleuronat, talc, sodium morrhuate, polythene, cellophane, and assorted acids and alkalies.

Localized experimental pericardial constrictions were produced in 1947, in dogs by Dr. George W. Duncan and one of us (J. P. I.) using plastic casts. The present method is a modification and further application of the plastic cast method.

Parsons and Holman (11) successfully utilized in stages a pericardial suture technic, Dakin's solution, and sodium morrhuate to induce localized pericardial scarring. They have reported results of constriction of the right auricle and of the right auricle and ventricle in dogs which closely agree with those reported here.

METHODS

Various pericardial constrictions were produced in seventy-nine mongrel male and female dogs weighing from 8.3 to 19.6 kilograms. They were maintained on standard kennel rations with horse meat and milk supplements. Feedings were voluntary. The animals were untreated except for (a) thoracentesis if necessary in the early postoperative period and occasionally in the chronic stage and (b) intramuscular penicillin when there was evidence of infection. Sixty-five per cent of the animals survived into the chronic phase of pericardial constriction. They died then either in the natural course of their disease, or by sacrifice, or during laboratory procedures. In fourteen animals the survival period was terminated by pericardiectomy experiments.

Anterolateral intercostal thoracotomy was performed with the dogs under ether anesthesia breathing by mechanical respirator (12). The fundamental steps of the method for producing localized pericardial constrictions were: (a) suture of the pericardium to the myocardium to

* From the Surgical Hunterian Laboratory of the Johns Hopkins University School of Medicine.

form a pericardial pocket over the desired area of future constriction and (b) introduction of a foregin body into the pericardial pocket to cause scarring.

As may be seen in Figures 1 and 2 the coronary arteries were utilized as landmarks for isolating the various pericardial pockets over (a) the right auricle and ventricle, (b) the left auricle and ventricle, (c) the right auricle alone, and (d) all the heart except the right auricle.

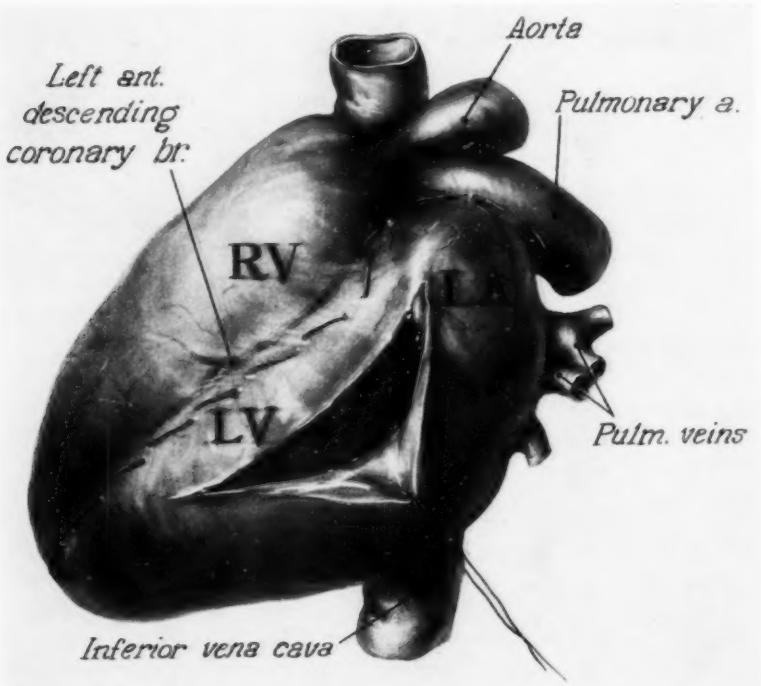


FIG. 1. This demonstrates how pericardial pockets were isolated over the left auricle and ventricle or over the right auricle and ventricle by suturing the pericardium to the myocardium along the anterior descending branch of the left coronary artery. Either side of the heart desired was then covered by a plastic cast, inserted into the pericardial pocket through an incision. Localized chronic pericardial scarring was thus produced.

A foreign body was then introduced into the prepared pericardial compartment. Copolymer vinyl acetate and vinyl chloride in acetone was injected by syringe and needle or inserted through a pericardial incision as a premolded cast. When injected, sufficient liquid plastic was used to form a thin layer within the chosen compartment. This plastic material though liquid in the acetone solvent solidifies flexibly in body fluids. The injection technic sometimes caused severe mediastinitis and massive hydrothroax (13). To avoid this, premolded casts were made by draping three single layers of sterile gauze over a heart shaped glass mold, saturating them with the liquid plastic, and allowing them to dry for fifteen minutes in order

for the acetone to evaporate. After being cut to fit, these casts were placed within the pericardial pocket through an incision. In Figure 2 such a cast is in position over the right auricle.

By omitting all suture lines and placing a larger cast within the whole pericardial sac, constriction of the whole heart was accomplished.

The pericardial space was drained into the pleural space.

After the operation in which the plastic cast was selectively situated the scarring process proceeded for varying periods from one to ten months.

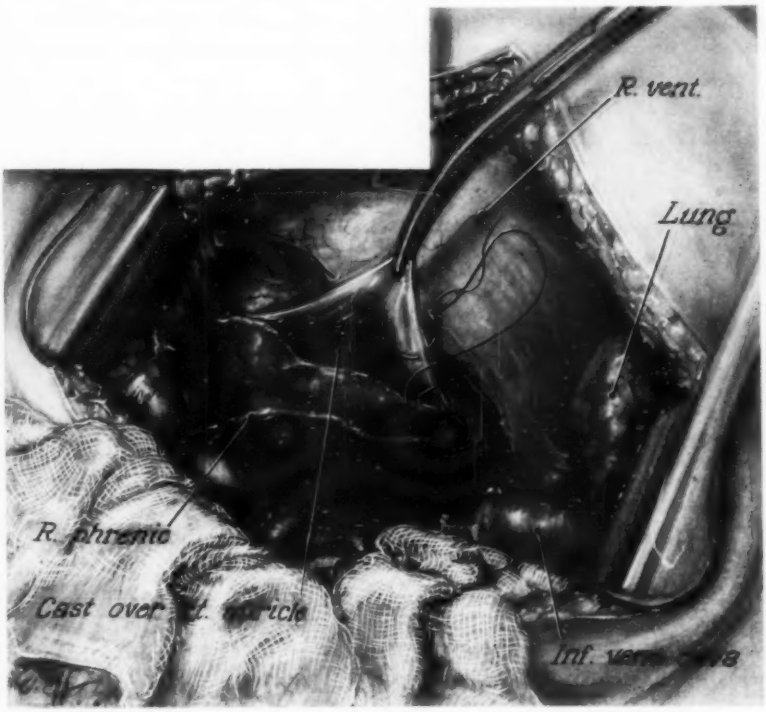


FIG. 2. Pericardial pockets were isolated over the right auricle or over all the heart except the right auricle by suturing the pericardium to the myocardium along the right coronary artery. A plastic cast was introduced into either pericardial compartment to cause chronic scarring. Such a cast is in place over the right auricle in this illustration.

Before and after pericardial constriction hemodynamic determinations were made with the dogs trained, unanesthetized, post-absorptive, unrestrained, supine, at rest for fifteen minutes or longer in a quiet room. Venous and arterial cardiac catheterizations were performed following the methods of Cournand (14) and Hellems et al. (15). Pressures in the jugular vein, right auricle, right ventricle, pulmonary artery, pulmonary "capillaries" (15), and femoral artery in all of the dogs and in the pulmonary vein, left auricle, and left ventricle in fourteen of the dogs were recorded by the Sanborn electrometer and Hathaway galvanometer and pressure gauges. The zero point was arbitrarily set at 7.5 centimeters anterior

to the skin of the back and corrected to the level of the right auricle at autopsy. Mean pressures were calculated by planimetric integration of pressure tracings or by electrical integration of the oscillographic tracings. Saline and mercury manometers were used routinely to check mean pressures.

The arterial cardiac catheterizations were carried out by advancing the catheters in a retrogade direction from the femoral artery under fluoroscopic observation. The aortic valve was breached by a gentle to and fro motion of the catheter, caution being taken not to thrust forward against resistance. The left oblique position aided both in directing and visualizing the catheter on its path into the left auricle Great care was required to avoid ventricular fibrillation caused by over-zealous manipulation or kinking of the catheter as

TABLE I

Results of Arterial Catheterizations

DOG NUMBER	LOCATION OF PERICARDIAL CONSTRICTION	MEAN PULMONARY "CAPILLARY" PRESSURE MM. Hg		MEAN PULMONARY VENOUS PRESSURE MM. Hg		MEAN LEFT AURICULAR PRESSURE MM. Hg		VARIATIONS BETWEEN PULMONARY "CAPILLARY" AND LEFT AURICULAR MEAN PRESSURES MM. Hg	
		Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper
VA #38	Left Heart	6	17	3	17	3	14	3	3
40	Left Heart	8	27	5	26	6	26	2	1
42	Left Heart	6	19	5	18	5	18	1	1
51	Left Heart	6		7		6		0	
52	Left Heart	10		7		8		2	
71	Left Heart	8	12	8	13	8	13	0	1
63	Right Heart	5		4		4		1	
66	Right Heart	10		12		10		0	
68	Right Heart	9		9		7		2	
72	Right Heart	8	8	6	6	5	6	3	2
78	Right Heart	7		6		6		1	
59	Whole Heart	9	9	8	9	7	8	2	1
60	Whole Heart	6	14	4	12	4	12	2	2
70	Whole Heart	8	21	6	22	6	20	2	1
Mean.....		8	16	6	15	6	14	2	2

it was advanced through the left ventricle. (There were three deaths in twenty-four arterial cardiac catheterizations.) In fourteen animals preoperatively and eight postoperatively two sets of simultaneous determinations were made with (a) one catheter wedged into a pulmonary arterial terminal and one lying in the left auricle, and (b) one catheter wedged into a pulmonary arterial terminal and one lying in a pulmonary vein (Table I). The correlation between pulmonary "capillary" pressure and left auricular pressure was significant, as previously reported by Dow and Gorlin (16) and Hellems et al. (15). For purposes of this study pulmonary "capillary" pressure was therefore used as an index of left auricular pressure.

Bing et al., Dexter et al., and Lagerlof and Werks have found this same relationship to exist in man (71, 72, 73).

When respiratory and pulse rates were stable, cardiac output was obtained by employing the direct Fick principle (17). Blood samples were drawn from the pulmonary and femoral arteries simultaneously or in rapid succession. Analysis of blood oxygen content, capacity,

and saturation was in accordance with the methods of Van Slyke and Neill (18). Oxygen consumption was measured with the Benedict-Roth spirometer with the aid of the Blalock mask (19). Cardiac index was calculated by dividing cardiac output in liters per minute by square meters of body surface area. Meeh's formula using Rubner's constant for the dog was applied in finding body surface area:

$$\frac{SA}{10{,}000} = 11.2W^{.667}$$

where SA is surface area in square meters and W is weight in grams.

Resistances were calculated according to the Poiseuille equation in which

$$\text{Resistance} = \frac{\text{Pressure gradient}}{\text{Rate of blood flow}}$$

Pulmonary "arteriolar" resistance was calculated thus:

$$PAR = \frac{PAm - \text{"P Cm"}}{CI}$$

Left ventricular resistance in diastole was calculated thus:

$$LVR = \frac{\text{"P Cm"} - 0}{CI}$$

Total systemic resistance was calculated thus:

$$TSR = \frac{FAm - 0}{CI}$$

Right ventricular resistance in diastole was calculated thus:

$$RVR = \frac{RAm - 0}{CI}$$

where PAm = pulmonary arterial mean pressure, mm. Hg
"P Cm" = pulmonary "capillary" mean pressure, mm. Hg
FAm = femoral arterial mean pressure, mm. Hg
CI = cardiac index, liters per minute per square meter of body surface area.

As Gorlin et al. (20) pointed out these calculations are based on the belief that resistance in the greater and lesser vascular circuits includes the resistance offered by the other ventricle in diastole. The ventricular resistance calculations are included since resistance offered by a ventricle constricted by pericardial scar has significant proportions.

The equations used for ventricular work are:

$$\text{RV work} = \frac{(PAm - RAm) \times 13.6 \times CI}{1000}$$

Kilogram meters per minute per square meter body surface

$$\text{LV work} = \frac{(FAm - \text{"PCm"*}) \times 13.6 \times CI}{1000}$$

Kilogram meters per minute per square meter body surface

where RV work = work of right ventricle against pressure
LV work = work of left ventricle against pressure
CI = cardiac index, liters per minute per square meter body surface area
13.6 = specific gravity of mercury
PAm = pulmonary arterial mean pressure, mm. Hg
RAm = right auricular mean pressure, mm. Hg (index of right ventricular filling pressure)
FAm = femoral arterial mean pressure, mm. Hg
"PCm" = pulmonary "capillary" mean pressure, mm. Hg (index of left ventricular filling pressure)

These work calculations are made with the understanding that they represent work against pressure; that is, work to accelerate blood is not included. Mean pulmonary and femoral arterial pressures are substituted for mean systolic ejection pressures (21), introducing a ten to forty per cent error in ventricular work against pressure (22), since peripheral work is being calculated. Account is taken that the ventricle elevates pressure only from its diastolic filling pressure to systolic ejection pressure (20), in order to avoid the appreciable error with elevated filling pressures in constrictive pericarditis. These calculations for work tell nothing about the drag effect which the pericardial scar may have on the myocardium during systolic contraction.

CONTROL DATA

Each dog served as its own control with the over-all data indicating the general scope of normal hemodynamic variations in these dogs. In general the control values agree with those reported elsewhere (15, 16, 23, 24, 25, 26, 27).

(Table II). Oxygen consumption varied from 61 to 154 cubic centimeters per minute with an average of 96, and arteriovenous difference ranged from 3.42 to 7.02 volumes per cent with an average of 4.57, while cardiac output varied between 1.3 and 3.4 liters per minute with an average of 2.1. Cardiac indices were in the range from 2.61 to 4.02, averaging 3.36 liters per minute per square meter of body surface.

In millimeters of mercury with all determinations averaged, the right auricular mean pressure was 1, right ventricular filling pressure 0, pulmonary arterial systolic pressure 27, diastolic 10, pulmonary arterial mean pressure 15, pulmonary "capillary" mean pressure 8, pulmonary venous mean pressure 6, left auricular mean pressure 6, and femoral arterial mean pressure 114.

CONSTRICTION OF THE RIGHT SIDE OF THE HEART

Nineteen animals had plastic casts placed over the right auricle and ventricle. Twelve of these developed chronic constriction localized to the casted area (Table III). Each of these twelve dogs presented the signs of systemic venous congestion, that is, elevated systemic venous pressure, hepatomegaly, ascites, peripheral edema, and hydrothorax.

The period with pericarditis may be divided into acute and chronic phases. The chronic phase entered a pre-terminal state of generalized cardiovascular

* Where direct left auricular mean pressures were measured, these were substituted for "PCm."

deterioration about forty-eight to seventy-two hours before death. Data obtained during the pre-terminal period are excluded in this study.

The sequence of changes following application of the plastic cast over the right side of the heart is outlined in Figure 3, based on the postoperative course of VA #78.

The first postoperative week of the acute phase of pericarditis was marked by elevation in peripheral and central venous pressure, tachycardia, increased cardiac output (Table IV) (28, 29), reduced arteriovenous difference, depressed systemic arterial pressure (30), and decreased systemic resistance. The

TABLE II

Resting Hemodynamic Values in Seventy-nine Normal Unanesthetized Dogs

	WEIGHT KILOGRAMS	SURFACE AREA SQUARE METERS	PULSE PER MINUTE	RESPIRATIONS PER MINUTE	OXYGEN CONSUMPTION CC/MIN.	ARTERIO VENOUS DIFFERENCE VOL. %	CARDIAC OUTPUT l/MIN.	CARDIAC INDEX l/MIN/M²	FEMORAL ARTERY MEAN MM. Hg
Highest	19.6	.816	152	32	154	7.02	3.40	4.02	150
Lowest	8.3	.460	64	11	61	3.42	1.30	2.61	94
Mean	13.2	.621	87	19	96	4.57	2.10	3.36	114
Number of determinations			525	525	260	104	104	104	305
Number of dogs	79	79	79	79	79	79	79	79	79

	JUGULAR VEIN MM. Hg	RIGHT AURICLE MEAN MM. Hg	RIGHT VENT. MM. Hg	PULMONARY ARTERY MM. Hg	PULMONARY ARTERY MEAN MM. Hg	PULMONARY "CAPILLARY" MEAN MM. Hg	GRADIENT PA_m-PC_m MM. Hg	PULMONARY VEIN MEAN MM. Hg	LEFT AURICLE MEAN MM. Hg
Highest	6	4	38/2	37/14	20	11	10	12	10
Lowest	0	−2	16/0	16/3	9	3	4	3	3
Mean	3	1	28/0	27/10	15	8	7	6	6
Number of determinations	186	104	104	104	104	67	67	14	14
Number of dogs	79	79	79	79	79	51	51	14	14

animals were anoretic during the first several days, and weight loss occurred. Fever was sometimes prominent.

Later in the first week the animals ate well. Usually the body weight increased, and peripheral edema or ascites became evident. Cardiac output continued at or slightly above control levels.

During the second week there was a spontaneous diuresis accompanied in most cases by weight loss. Systemic venous pressure continued to be elevated, but dropped from previous peak levels. This was considered the end of the acute stage of pericarditis.

During the ensuing one to three months there followed a chronic phase of

slowly progressive constrictive pericarditis with a sustained period of elevated systemic venous pressure, but normal systemic arterial pulse pressure, cardiac output, oxygen consumption, and arteriovenous difference. Hepatomegaly and ascites became prominent. Hepatic enlargement and chronic passive congestion are demonstrated by Figures 4 and 5.

TABLE III

Summary of Pericardial Constriction Experiments

LOCATION OF PERICARDIAL CONSTRICTION	NO. OF DOGS USED	VINYL ACETATE INJECTION METHOD			VINYL ACETATE GAUZE CAST METHOD			TOTAL NO. CHRONIC SURVIVORS AV.	AV. NO. OF DAYS SURVIVED	REMARKS
		No. prepared	No. chronic survivors	Days survived av.	No. prepared	No. chronic survivors	Days survived av.			
Right auricle	12	5	3	*	7	7	*	10	Indefinite	No change in hemodynamics
Right auricle ventricle	19	9	4	53	10	8	138	12	97	Elevated systemic venous pressure, hepatomegaly, ascites
Both ventricles and left auricle	15	5	2	36	10	6	71	8	62	Elevated systematic venous pressure, hepatomegaly, ascites, pulmonary hypertension
Whole heart†	14	2	1	27	12	9	60	10	54	Elevated systemic veuous pressure, hepatomegaly, ascites, pulmonary hypertension
Left auricle and ventricle‡	19	6	2	78	13	10	119	12	123	Pulmonary hypertension, rales, accenttuated P_2, pulmonary edema
Totals.....	79	27	12 (44%)	—	52	40 (77%)	—	52 (65%)	—	

* Sacrificed at 6–10 months.

† Most of these animals were used for pericardiectomy experiments.

‡ One animal also developed elevated systematic venous pressure and peripheral edema.

Later in the chronic phase cardiac output gradually decreased with a widened arteriovenous difference and normal oxygen consumption. Systemic venous pressure (peripheral and central) rose further with a reduced peripheral-central pressure gradient. Except for the early postoperative depression, systemic arterial pressure was maintained with slight narrowing of pulse

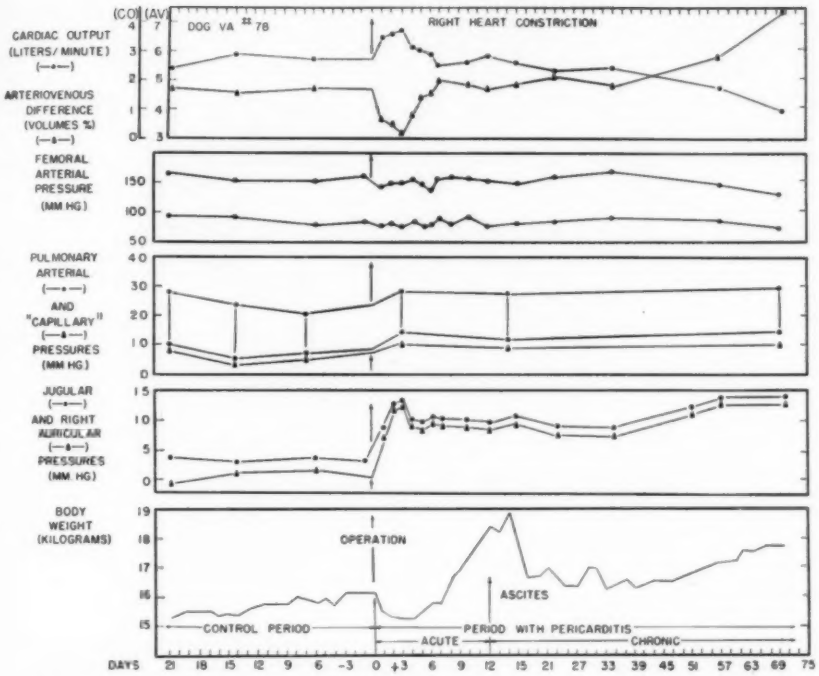

(CO) (AV)
DOG VA 78
RIGHT HEART CONSTRICTION
CARDIAC OUTPUT (LITERS/MINUTE)
ARTERIOVENOUS DIFFERENCE (VOLUMES %)
FEMORAL ARTERIAL PRESSURE (MM HG)
PULMONARY ARTERIAL AND "CAPILLARY" PRESSURES (MM HG)
JUGULAR AND RIGHT AURICULAR PRESSURES (MM HG)
BODY WEIGHT (KILOGRAMS)
OPERATION
ASCITES
CONTROL PERIOD
PERIOD WITH PERICARDITIS
ACUTE
CHRONIC
DAYS
21 18 15 12 9 6 -3 0 +3 6 9 12 15 21 27 33 39 45 51 57 63 69 75

FIG. 3. The sequence of hemodynamic changes associated with localized chronic pericardial constriction of the right auricle and ventricle is presented in these curves of cardiac output and systemic and pulmonary blood pressures. Systemic venous pressure rose while pulmonary pressures remained unchanged. Note that with normal resting cardiac output and elevated systemic venous pressure increased body weight and ascites appeared. There was a spontaneous diuresis at about two weeks after application of the pericardial cast which marked the end of the acute stage of pericarditis.

TABLE IV

Cardiac Index in the Early Postoperative Period Following Insertion of Pericardial Cast

DOG VA#	LOCATION OF CAST (SIDE OF HEART)	CARDIAC INDEX (LITERS/MINUTE/M²)									MAXIMUM POST-OPERATIVE INCREASE IN CARDIAC INDEX %
		Preoperative weeks				Postoperative days					
		3	2	1	Control mean	1	3	5	7	10	
66	Right		3.18	2.74	2.96	3.68	3.35	3.35	3.00	3.21	30.1
78	Right	3.31	3.90	3.47	3.56	4.88	5.30	4.17	3.96	3.80	48.9
70	Whole	3.34		2.81	3.08	4.33	3.76	3.87	3.26	3.52	40.6
75	Whole	3.48	2.82	3.68	3.32	5.46	5.31	4.60	3.98	3.19	64.5
71	Left		3.52	4.07	3.80	4.60	4.55	3.93	4.18	3.70	21.1
Mean....					3.34	4.39	4.55	4.00	3.66	3.48	39.0

FIG. 4. An enlarged, congested liver, covered with whitish fibrin deposits, as illustrated in this photograph of the liver from dog, VA #9, was found at post mortem in all dogs with chronic pericardial constriction of the right ventricle.

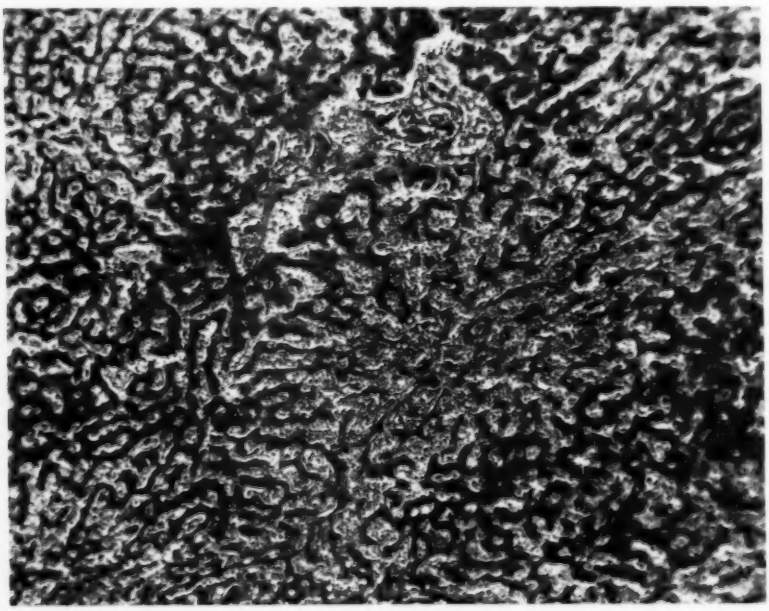


FIG. 5. This photomicrograph shows the chronic passive congestion of the liver which occurred whenever the right ventricle was encased in pericardial scar (VA # 4).

pressure until the pre-terminal phase when it fell markedly. Pulmonary arterial pressure remained normal, and pulmonary edema did not occur. In the chronic phase the body weight increased with massive ascites, peripheral edema, and hydrothorax, but in the last several weeks of survival, because of reduced food intake, weight remained constant or declined in spite of increasing ascites and peripheral edema.

FIGS. 6, 7, and 8. These post mortem photographs of dog heart, VA #78, show the thick pericardial scar over the right auricle and ventricle with the plastic cast lying between the scarred parietal pericardium and epicardium. The epicardium of the left ventricle is glistening and unscarred, and the overlying parietal pericardium is transparent.

Photographs of hearts from dogs VA #25 and VA #66 display the thickening of the parietal pericardium (six to fourteen millimeters) over the right auricle and ventricle with the plastic cast beneath (Figs. 6, 7, 8, 9, 10). The epicardial thickening under the cast was two to eight millimeters deep. Figure 11 shows the pericardial scarring microscopically.

In order to contrast control hemodynamic values with those found in the phase of chronic constriction, Tables V and VI have been compiled. Table V summarizes cardiac output data which is divided into three sections. The first section represents the pre-operative data. The second section is data obtained

FIG. 7

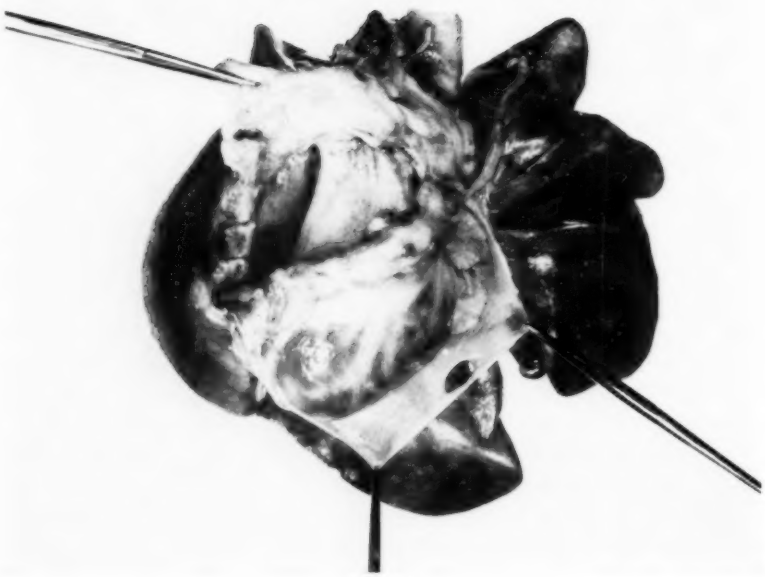
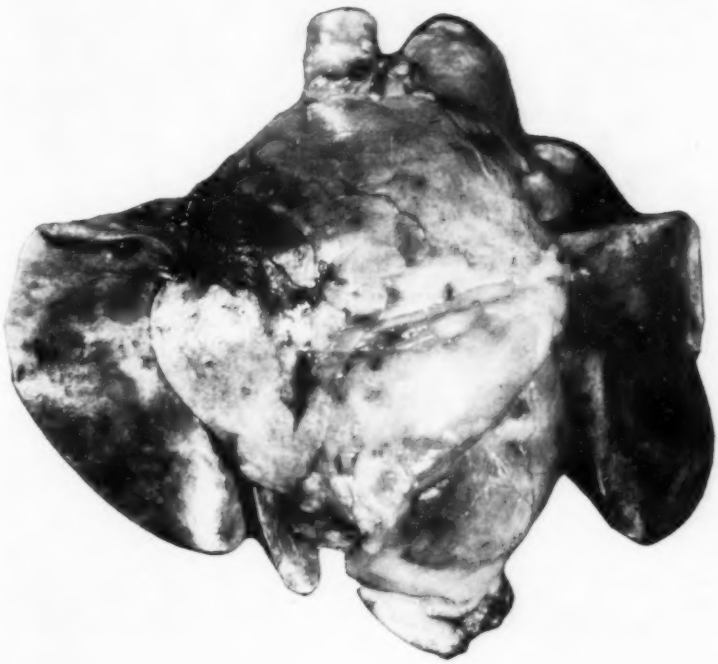


FIG. 8

early during the chronic phase of pericardial constriction (3–6 weeks postoperative). The third section is data from late in the chronic phase (6–30 weeks). The mean AV difference of all the animals during the control period was 4.50 volumes per cent. This rose to 5.63 early in the chronic phase and to 9.89 late in the chronic phase. At similar intervals there were reductions in mean cardiac index from 3.50 to 3.07 to 2.08 liters per minute per square



FIGS. 9 and 10. These photographs of dog heart, VA #25, reveal the pericardial scarring and plastic cast in place over the right auricle and ventricle with the normal pericardium and epicardium over the left auricle and ventricle.

meter of body surface area. The mean oxygen consumption remained essentially constant (97, 103, and 103 cubic centimeters per minute).

Table VI summarizes the pressure and ventricular work data. This is divided into pre- and postoperative columns. The mean preoperative control values are listed, as are the latest postoperative values. The latter were obtained at somewhat different intervals in different dogs, but always at times when the chronic syndrome was established in each dog (four weeks to four months) and before the pre-terminal collapse.

FIG. 10

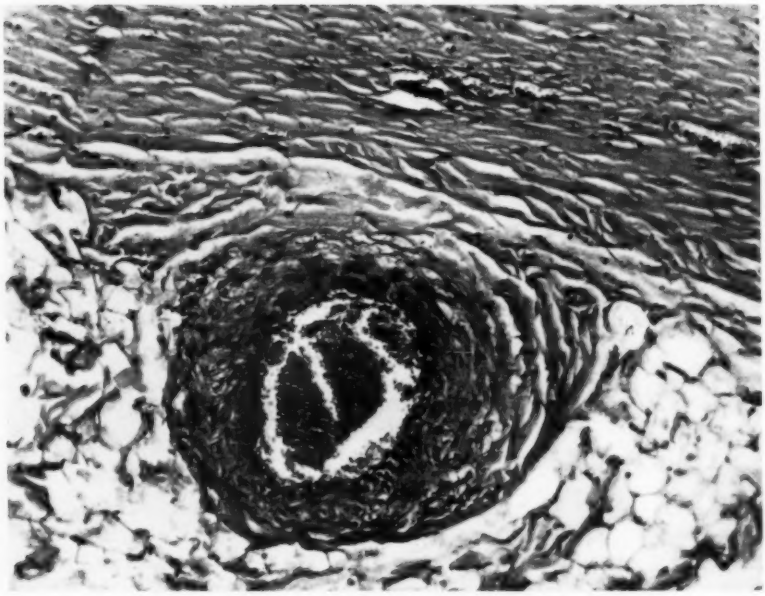


FIG. 11. This shows the epicardial scarring resulting from the introduction of a plastic cast into the pericardial cavity. A coronary artery is seen beneath the scarred epicardium.

TABLE V

Oxygen Consumption, A - V Difference, Cardiac Output, Cardiac Index, and Stroke Volume in Dogs with Constriction of the Right Auricle and Ventricle

DOG NUMBER	PREOPERATIVE (CONTROL)						POSTOPERATIVE (<6 WEEKS)						POSTOPERATIVE (>6 WEEKS)					
	Pulse Rate	O_2 Cons. cc/min	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke	Pulse Rate	O_2 Cons. cc/min.	A-V. Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke	Pulse Rate	O_2 Cons. cc/min	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke
VA# 4	96	82	4.40	1.86	4.00	19							124	113	10.54	1.01	2.16	8
	88	74	5.23	1.41	3.02	16												
5	68	95	4.63	2.05	3.25	30							118	88	6.84	1.29	2.04	11
	82	112	4.69	2.39	3.78	29												
6	102	87	3.98	2.14	3.65	22	125	87	8.84	0.98	1.63	10						
	90	84	3.42	2.46	4.11	27												
9	86	84	4.34	1.93	3.17	22	110	91	8.07	1.13	1.86	10						
	78	113	5.21	2.17	3.56	28												
15	90	91	4.39	2.18	3.79	24	88	90	6.25	1.44	2.84	16	113	83	9.16	0.90	1.60	8
	82	75	4.56	1.64	2.90	20												
20	74	75	3.68	2.04	3.62	28	82	95	5.91	1.61	2.59	20	130	86	7.26	1.18	2.10	9
	78	93	5.32	1.75	3.18	22												
25	70	98	4.10	2.39	3.49	34	80	112	4.87	2.30	3.37	29	106	105	8.32	1.26	1.84	12
63	98	129	5.36	2.40	3.22	24	100	133	4.96	2.68	3.60	27	141	130	9.50	1.37	1.86	10
	91	141	4.81	2.93	3.95	32							150	130	10.39	1.25	1.68	8
66	84	67	4.67	1.43	2.74	17	97	81	5.48	1.48	3.19	15	122	72	8.65	0.83	1.59	7
	66	75	4.52	1.66	3.18	25												
68	74	102	4.53	2.25	3.85	30	85	111	5.06	2.19	3.83	26	127	113	8.01	1.31	2.29	10
72	85	111	4.02	2.76	3.98	33	92	108	3.82	2.83	4.08	31	105	96	6.57	1.44	2.07	14
	87	97	4.11	2.36	3.38	27	96	95	4.57	2.08	3.00	22						
78	91	109	4.63	2.35	3.31	25	86	125	5.23	2.39	3.35	28	116	110	5.92	1.86	2.62	16
	105	122	4.38	2.79	3.90	26	108	113	4.50	2.51	3.52	23	139	114	7.70	1.48	2.07	7
	79	116	4.47	2.55	3.47	32												
Mean.....	86	97	4.50	2.16	3.50	25	96	103	5.63	1.83	3.07	21	124	103	9.89	1.18	2.08	10

TABLE VI

Pressures and Ventricular Work Against Pressure in Dogs with Constriction of the Right Auricle and Ventricle

DOG NUMBER	JUGULAR VEIN MM. Hg		RIGHT AURICLE MEAN MM. Hg		RIGHT VENTRICLE MM. Hg		PULMONARY ARTERY MM. Hg		PULMONARY ARTERY MEAN MM. Hg		PULMONARY "CAPILLARY" MEAN MM. Hg		CARDIAC INDEX L/MIN/M²		RIGHT VENTRICULAR WORK AGAINST PRESSURE KILOGRAM METERS/MIN./M²		LEFT VENTRICULAR WORK AGAINST PRESSURE KILOGRAM METERS/MIN./M²		FEMORAL ARTERY MEAN MM. Hg	
	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper
VA # 4	1	15	−1	15	27/1	30/15	27/12	28/15	19	18	10	9	3.51	2.16	0.95	0.09	5.97	3.26	131	116
5	5	13	2	12	25/0	23/12	24/10	20/13	15	15	8	7	3.52	2.04	0.62	0.08	4.98	2.55	110	98
6	4	11	1	10	30/0	26/10	30/10	26/12	18	13	9	8	3.88	1.63	0.90	0.07	6.34	2.41	126	114
9	4	10	2	9	27/2	24/9	25/8	24/11	16	13	7	8	3.36	1.86	0.64	0.10	5.02	2.66	116	109
15	1	12	0	11	23/0	18/9	23/11	19/14	13	15	9	9	3.34	1.60	0.59	0.09	4.59	1.96	105	96
20	3	13	1	13	26/0	33/12	25/7	25/15	17	16	8	9	3.40	2.10	0.74	0.09	5.04	3.06	115	112
25	3	10	0	9	32/0	36/9	32/9	36/12	16	17	11	10	3.49	1.84	0.76	0.20	5.46	2.83	121	115
63	4	16	2	16	24/0	31/14	23/7	26/15	13	17	5	9	3.58	1.68	0.54	0.02	4.67	2.19	102	100
66	2	12	0	11	26/0	26/11	25/12	23/11	16	14	10	9	2.96	1.59	0.64	0.06	4.51	2.40	118	118
68	2	10	1	9	29/0	27/8	28/11	27/13	18	16	9	7	3.85	2.29	0.89	0.22	7.02	3.72	140	125
72	0	11	−1	11	25/1	25/10	24/12	25/13	15	14	8	8	3.68	2.07	0.80	0.08	5.51	3.10	116	112
78	3	14	1	12	26/0	35/12	23/8	29/14	17	17	7	10	3.56	2.07	0.77	0.14	5.18	2.96	113	110
Mean	3	12	1	11	27/0	28/11	26/10	26/13	16	15	8	9	3.51	1.92	0.74	0.10	5.36	2.76	118	109

The average systemic venous pressure rose from 3 millimeters of mercury to 12. The right auricular mean pressures averaged 1 millimeter of mercury preoperatively, 11 postoperatively. The average right ventricular end-diastolic pressure increased from 0 millimeters of mercury to 11. Since the systolic pressure was essentially unchanged, right ventricular pulse pressure narrowed markedly. This has been observed with cardiac tamponade (31, 32) and in some cases of constrictive pericarditis (33). The pulmonary and femoral arterial pressures were not significantly altered.

The average right ventricular work against pressure fell markedly from the control value of 0.74 kilogram meters per minute per square meter of body surface area to 0.10. Left ventricular work against pressure fell from 5.36 kilogram meters per minute per square meter of body surface area to 2.76 as a result of the decrease in cardiac index.

TABLE VII

Comparison of Average Cardiovascular Resistances in Dogs Before and After Various Pericardial Constrictions

MEAN RESISTANCES (MM. Hg/L./MIN./M²)	CONTROL	LOCATION OF CONSTRICTION		
		Right auricle and ventricle	Left auricle and ventricle	Whole heart
Left ventricular resistance in diastole	2.4	3.1	8.1	9.4
Pulmonary "arteriolar" resistance	2.1	4.7	7.6	6.0
Total systemic resistance	33.9	56.8	46.0	59.1
Right ventricular resistance in diastole	0.3	5.7	1.2	7.2
Number of dogs	34	12	12	10

Table VII lists the various resistances calculated according to equations described under METHODS. The second column represents the mean of the resistances of all dogs with constriction of the right auricle and ventricle. Pulmonary "arteriolar" resistance and systemic resistance increased in proportion to the decrease in cardiac output without significant change in pressure relationships. The striking change occurred in right ventricular resistance in diastole which increased from 0.3 millimeters of mercury per liter per square meter of body surface in the control period to 5.7 in the chronic phase.

Results of pericardiectomy

In three of the dogs with constriction of the right auricle and ventricle the pericardial scar (including epicardial scar) was removed. VA #4 had constriction for thirteen weeks at the time of pericardiectomy. The thick localized right parietal pericardial scar and cast were easily removed. The epicardial scar beneath measured three to four millimeters in thickness. By sharp dissection it was excised except along the right coronary artery where it was

divided at intervals to allow for diastolic expansion. In a period of ten days ascites disappeared, and the venous pressure fell to two millimeters of mercury. At autopsy twenty weeks later the right ventricular myocardium was normal in appearance.

The same procedure was carried out in two additional dogs, VA #15 and VA #20, with similar results. A fourth animal died during anesthetic induction.

Discussion

In clinical constrictive pericarditis a definite etiology is often impossible to establish (34), though infection with the tubercle bacillus has been proven most frequently (35, 36). Assuming that the majority of clinical cases result from bacterial inflammation with scarring, several effects of such inflammation and scarring must be considered in the analysis of the pathologic physiology of this condition. Not only the mechanical handicap of ventricular diastolic filling and drag effect upon ventricular systolic contraction, but myocarditis and myocardial fibrosis and atrophy may play individual or combined roles each in quantitatively varying degrees. Evaluation of these handicaps separately is a difficult if not impossible task. In those clinical cases where adequate removal of the pericardial scar has been considered accomplished and cure has not resulted, myocardial factors have been implicated. Though myocardial factors may well have been operating in these patients, question of adequacy of scar excision remains, since it may be hazardous or impossible to removal all of the epicardial scar, and since criteria of what constitutes adequacy of pericardiectomy have been unsettled (11, 37, 38).

In this series of experiments in which sterile fibroplastic reaction in the pericardial sac was initiated overlying a normal myocardium the objective was to induce pericardial limitation of the heart with a minimum of myocardial disease, so that the part played by pericardial limitation in the pathologic physiology of constrictive pericarditis might be investigated. A second objective was to localize the pericardial constriction in order to define the roles of various chambers of the heart in the pathologic physiology.

Theoretically a right ventricular volume-elasticity curve may be constructed by plotting right ventricular diastolic pressure against the related right ventricular diastolic blood volume, the curve sloping upwards as pressure increases with increasing volume. As the normal right ventricle with normal pericardium becomes fuller, greater elastic resistance is offered by the myocardium and pericardium within physiological limits, gradually necessitating large increases in pressure to effect small increases in volume. If the pericardium is thickened by scar so that it offers more elastic resistance than usual, as the right ventricle fills against this increased resistance greater than usual pressures corresponding to volume are required. Such volume-elasticity curves have been obtained post mortem from dog ventricles with and without pericardial

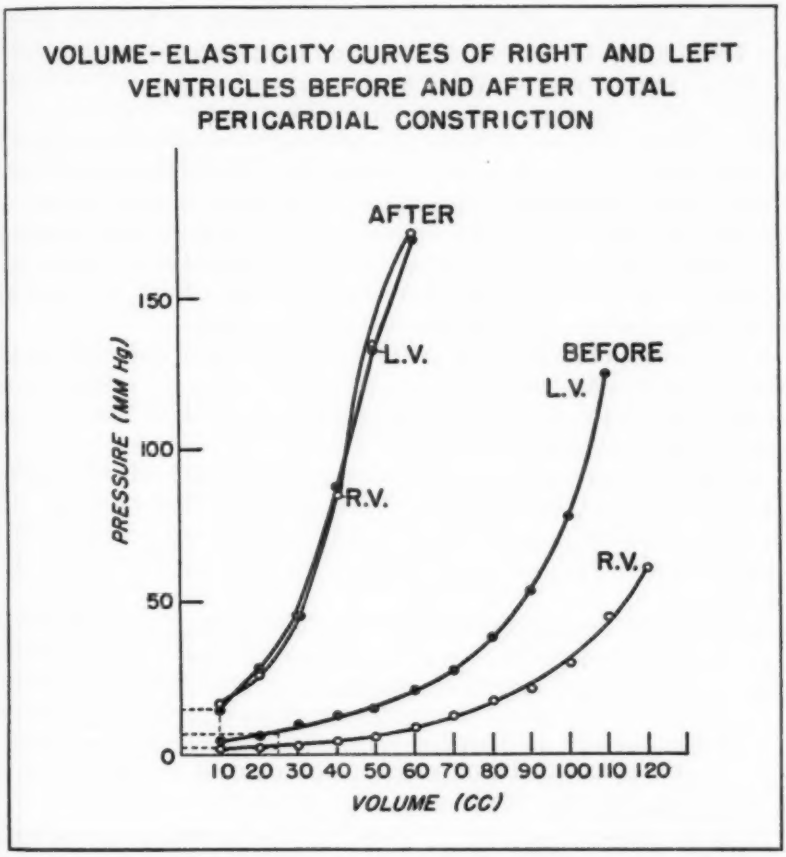


FIG. 12. These are volume-pressure curves obtained immediately after death from the right and left ventricles of the dog's heart within a normal pericardium and from the right and left ventricles within a generalized pericardial constriction. Increments of 10 cc. of saline were injected via the pulmonary artery or aorta into the closed ventricle, while intraventricular pressures were recorded with the Sanborn electrometer. It is of interest to compare the ventricular pressure-volume relationships before and after death. At a volume of 25 cc, which was the average stroke volume for this group of dogs, the pressures in the dead right and left ventricle were 1–2 and 6–7 millimeters of mercury respectively. Average end-diastolic pressures in the normal right and left ventricles during life were 0 and 6 millimeters of mercury respectively. At a volume of 10 cc, which was the average stroke volume for the group of dogs with generalized constrictive pericarditis, the pressures in the dead, constricted right and left ventricles were about 15 millimeters of mercury. Average end-diastolic pressures in the live, constricted right and left ventricles were 12 and 17 millimeters of mercury respectively. (*In vivo* pressures quoted above are uncorrected for intrathoracic base line).

constriction (39) (Fig. 12). Starling obtained similar curves with turtle hearts (40).

Thus in the dogs with chronic pericardial constriction of the right auricle and ventricle one may visualize that the first alteration came in the volume-elasticity characteristics of these chambers. A handicap in right ventricular diastolic filling was created wherein greater filling pressure was required to return a volume of blood to this chamber sufficient to maintain cardiac output. An index of the filling handicap and conversely of the function of compensatory venous return mechanisms is the degree of elevation of right ventricular end-diastolic, right auricular, and systemic venous pressures. These elevations are brought about via homeostatic mechanisms which probably depend upon volume-elasticity of the vascular system (vascular tone) (41, 42, 43) and total blood volume (45, 46, 47), including blood reservoirs (44).

With the compensatory rise in systemic venous pressure and while resting cardiac output and plasma protein concentration were yet normal, hepatomegaly and ascites developed, apparently on a hydrostatic basis, as suggested by the experiments of Starling (48, 49).

This ascites is apart from the early postoperative fluid and sodium retention pointed out by the balance studies of Davis et al. (8). Their work was with dogs with pericardial constriction, produced in a comparable manner. They explain this early fluid and sodium retention on the basis of adrenal cortical factors.

As the scarring proceeded and compensatory mechanisms presumably failed, the resting cardiac output fell. The pulse rate rose and stroke volume declined. Right ventricular work against pressure decreased in the extreme. Systemic and pulmonary arterial mean pressures though down slightly were supported by increased systemic and pulmonary "arteriolar" resistances respectively. Right ventricular resistance in diastole increased greatly due to the scar, while left ventricular resistance in diastole was little changed.

These alterations of hemodynamics were reversed by removal of the right ventricular pericardial scar, demonstrating that myocardial function was good.

CONSTRICTION OF THE LEFT SIDE OF THE HEART

Nineteen dogs had casts placed over the left auricle and ventricle. Twelve survived for long periods and developed chronic constriction localized to the casted area (Table III). These survivors were different from dogs with constriction of the right auricle and ventricle in that they had accentuation of the second pulmonic sound, rales in the lungs, and pulmonary hypertension by direct measurement, without signs of systemic venous congestion.

As illustrated by dog VA #52 (Fig. 13), systemic venous pressure did not rise in the acute stage. Cardiac output was elevated during the first week. Poor food intake with early weight loss was noted as with the dogs with constriction of the right side of the heart, but subsequent marked weight gain and ascites did not appear. Pulmonary arterial pressure was found to be

elevated early in the acute phase, and rales were sometimes auscultable at this time.

Quite a long period (one to six months) of apparent good health then intervened in which the dogs were very active and ate well. Except for a progressive increase in the pulmonary arterial and "capillary" pressures other hemodynamic values remained within control range.

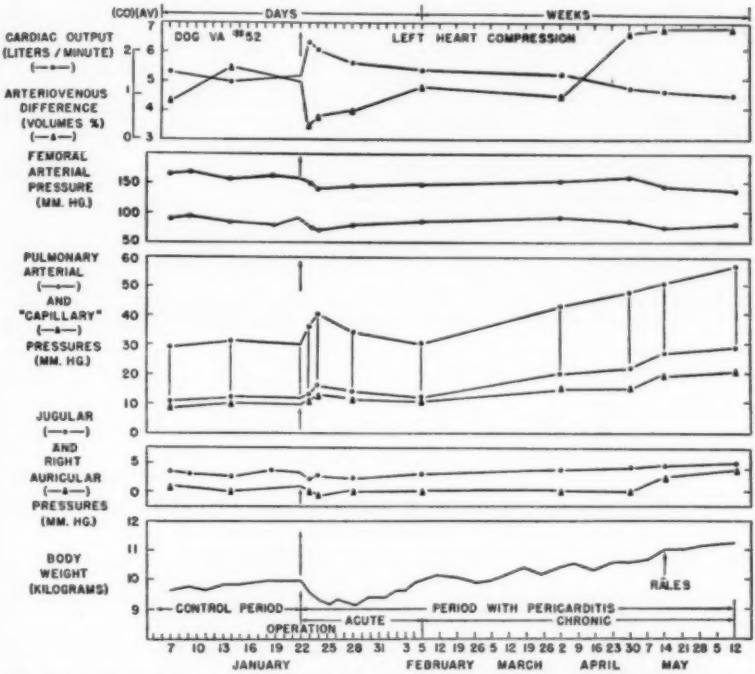


FIG. 13. The sequence of hemodynamic changes which accompanied localized chronic pericardial constriction of the left auricle and ventricle is presented in these curves of cardiac output and systemic and pulmonary blood pressures Systemic venous pressure remained normal while pulmonary pressures rose. No ascites developed, but rales were heard in the lungs, especially after exercise or excitement

In the chronic stage after about three to nine months the cardiac output diminished with a widened arteriovenous difference. Pulmonary hypertension as measured by arterial (Table I) as well as venous cardiac catheterization became marked. Fluoroscopic and electrokymographic examinations (Fig. 14) (50, 51, 52, 53) revealed active movements of the right cardiac border and diminished movements of the left cardiac border. Rales were frequently audible, especially after periods of excitement or exercise. The pulmonic second sound became accentuated. Systemic venous pressure and right ventricular

filling pressure were either not at all or only mildly elevated. Hepatomegaly, ascites, and hydrothorax did not appear. Five dogs, VA #71, 51, 34, 41, 35, died during this stage in acute pulmonary edema (Fig. 15). One of these, VA #35, at autopsy had a sizable localized collection of fluid under the cast.

In the case of dog VA #40, which survived eight months, right ventricular function became insufficient, and systemic venous pressure rose to 9 milli-

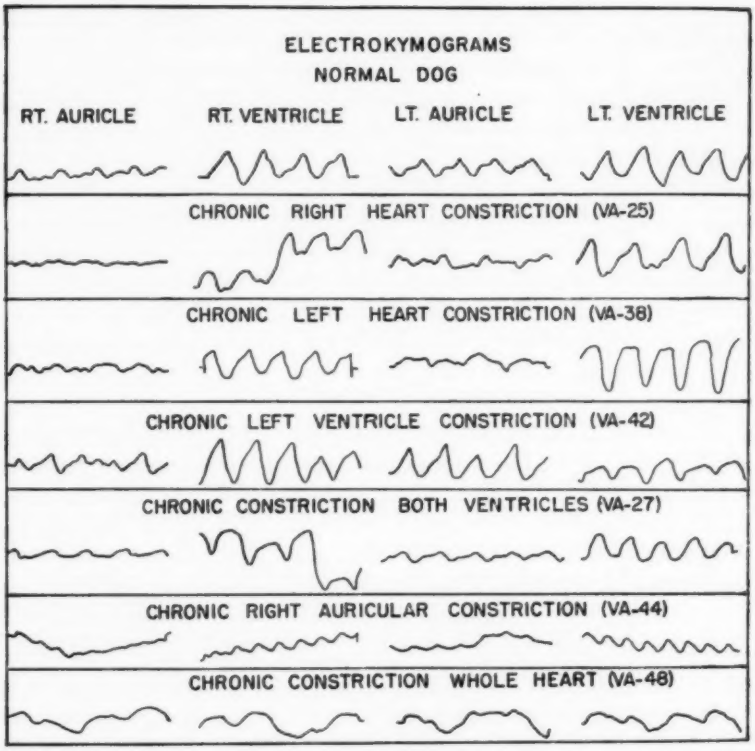


FIG. 14. These electrokymograms were made by Dr. Russell H. Morgan, Department of Radiology, The Johns Hopkins Hospital. Right auricle and left auricle are used to designate recordings taken from the area high on the right or left border of the heart respectively. The pathognomonic "flat-tops" and "V's" appear especially prominent in the left ventricular curve of VA #38. These recordings are on curvilinear coordinates.

meters of mercury. Peripheral edema appeared. Fluid was found in the peritoneal and pleural cavities post mortem. The lungs contained edema fluid and the liver was congested, a combination of pulmonary and systemic congestion.

Photographs of the hearts from dogs VA #40 and VA #41 (Figs. 16, 17, and 18) demonstrate the heavy pericardial scarring over the left side of the heart.

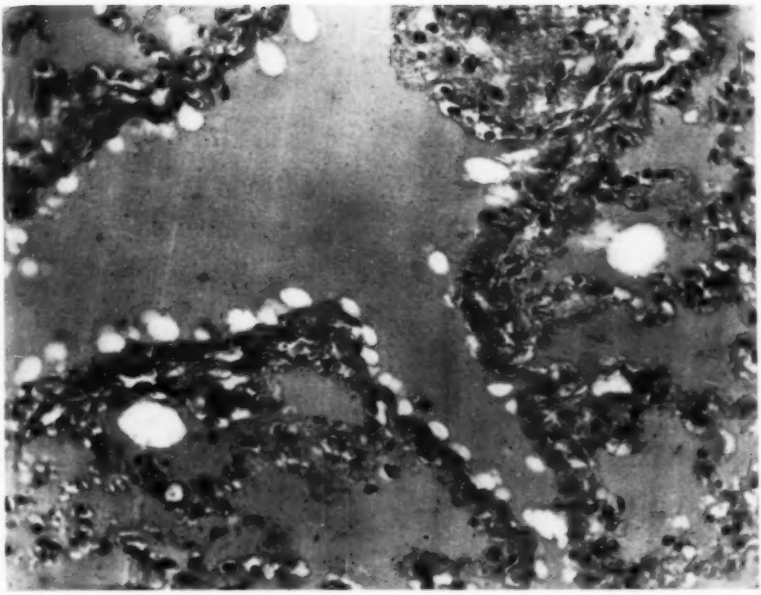


FIG. 15. This is a photomicrograph demonstrating the pulmonary edema which developed in dogs with localized pericardial constriction of the left auricle and ventricle (Dog VA # 40).

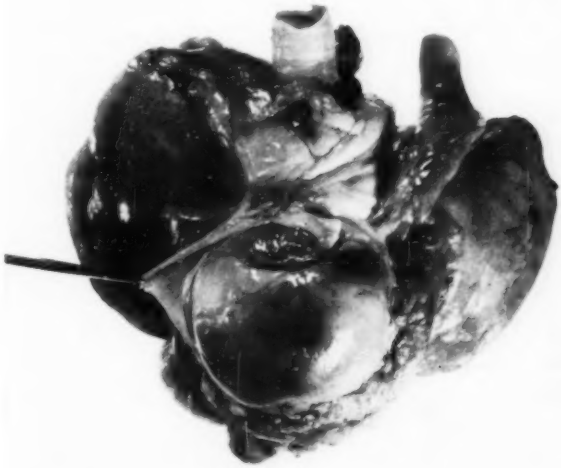


FIG. 16. The scarred pericardium encasing the left auricle and ventricle is contrasted with the normal pericardium and epicardium of the right auricle and ventricle in dog heart, VA # 40.

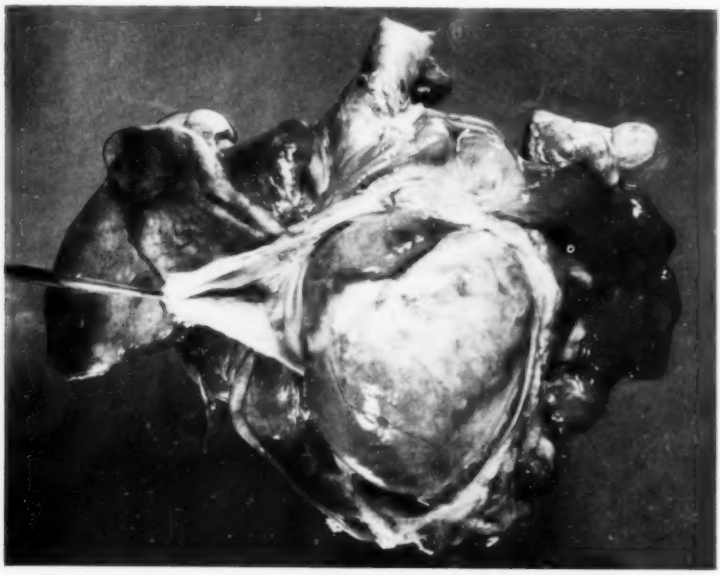
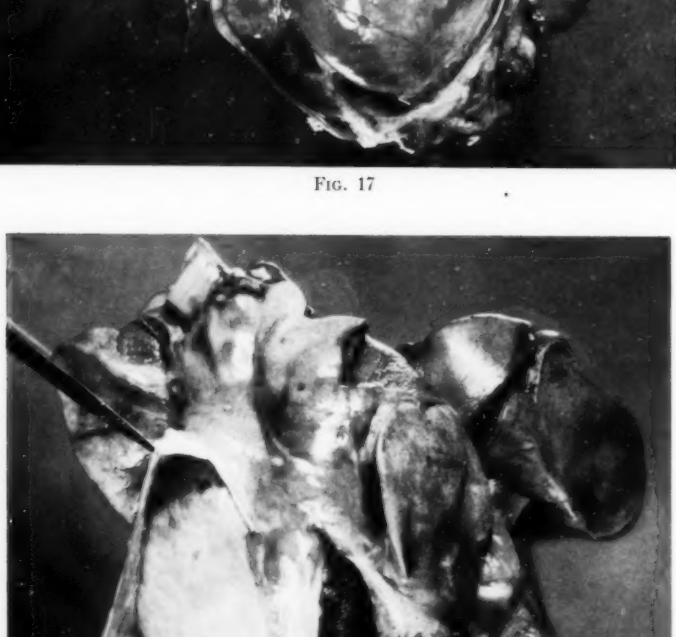


FIG. 17



FIGS. 17 and 18. The heavy pericardial scarring surrounding the plastic cast which is situated over the left auricle and ventricle is evident in these pictures of dog heart, VA #41.

Table VIII contains a summary of cardiac output values arbitrarily grouped into three periods: preoperative, first twelve weeks postoperative, and more than twelve weeks postoperative.

Average oxygen comsumption showed only slight change (preoperative, 93 cubic centimeters per minute, first twelve weeks, 98; therafter, 104). Average arteriovenous difference rose from 4.37 volumes per cent to 6.01 during the first twelve weeks and to 6.79 after the twelfth week. During these periods the average cardiac index fell from 3.47 liters per minute per square meter of body surface to 2.90 and then to 2.54. The over-all fall was not as great as with the dogs with constriction of the right half of the heart and took longer to occur.

(Table IX). The systemic venous pressure showed little average change, though in certain dogs that lived longer, a definite rise was noted. In ten of twelve dogs the trend was upwards. On the average, right auricular mean pressures also changed little, but again larger increases were recorded in particular dogs (VA #38, 40, 41, and 79), and an upward trend was apparent.

There were large average increases in right ventricular systolic and in all pulmonary pressures. The average of the pulmonary arterial mean pressures was 39 millimeters of mercury. The average of the pulmonary "capillary" mean pressures was 20.

Of note is the fact that average right ventricular work against pressure rose from 0.67 kilogram meters per minute per square meter to a value of 1.17. Average left ventricular work against pressure declined from 5.21 kilogram meters per minute per square meter of body surface area to 3.19.

(Table VII). Both left ventricular resistance in diastole and pulmonary "arteriolar" resistance increased. Average total systemic resistance increased somewhat. Right ventricular resistance in diastole varied only slightly from the control value.

Results of pericardiectomy

One dog, VA #42, was given a pericardiectomy after having had constriction of the left auricle and ventricle for twenty-one weeks. Before pericardiectomy, pulmonary arterial and "capillary" mean pressures had risen to 42 and 19 millimeters of mercury, respectively, and cardiac index had dropped to 2.33 liters per minute per square meter of body surface area. Pulmonary "arteriolar" resistance was calculated as 9.9 millimeters of mercury per liter per minute per square meter of body surface area. Six weeks following excision of the pericardial cast and scar overlying the left auricle and ventricle, pulmonary arterial and "capillary" mean pressures had fallen to 21 and 13 millimeters of mercury, respectively, and resting cardiac index was found to be 2.86 liters per minute per square meter of body surface area. Pulmonary "arteriolar" resistance was then nearly normal at 2.8 millimeters of mercury per minute per square meter of body surface area.

TABLE VIII

Oxygen Consumption, A - V Difference, Cardiac Output, Cardiac Index, and Stroke Volume in Dogs with Constriction of the Left Auricle and Ventricle

DOG NUMBER	PREOPERATIVE (CONTROL)						POSTOPERATIVE(<12 WEEKS)						POSTOPERATIVE (>12 WEEKS)					
	Pulse	O_2 Cons. cc/min.	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M_2	S.V. cc/ stroke	Pulse	O_2 Cons. cc/min.	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke	Pulse	O_2 Cons. cc/min.	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke
VA #12	80	87	3.49	2.49	3.95	31	100	128	7.96	1.61	2.54	16						
	84	110	5.12	2.14	3.35	26												
32	103	92	4.00	2.30	3.61	22	122	138	9.16	1.51	2.37	12						
35	94	90	3.98	2.26	3.69	24	113	108	5.29	2.04	3.01	18						
38	85	127	4.71	2.70	3.48	32	92	118	5.08	2.32	2.94	25	94	130	5.76	2.25	2.73	24
													117	126	7.98	1.57	1.84	13
39	88	124	5.13	2.41	3.44	27	95	136	6.28	2.16	3.08	23	102	132	6.56	2.01	2.92	20
40	76	109	4.21	2.59	3.56	34	84	121	5.30	2.28	3.25	27	91	125	6.47	1.93	2.85	21
													122	133	8.92	1.49	2.29	12
41	83	125	4.08	3.06	3.81	37	105	144	6.95	2.07	2.78	20						
42	78	92	4.52	2.03	3.11	26	94	99	5.94	1.76	2.72	19	98	100	6.93	1.44	2.33	15
51	96	78	4.25	1.83	3.72	19	86	71	4.33	1.64	3.33	20	104	86	5.66	1.51	3.06	14
	100	68	4.14	1.64	3.33	16	94	83	5.41	1.53	3.10	16	110	88	6.75	1.30	2.64	12
52	69	68	4.36	1.56	3.30	22	80	75	4.86	1.54	3.25	19	83	73	5.97	1.22	2.58	15
	78	74	5.63	1.31	2.78	17	92	67	4.53	1.47	3.11	16	100	80	6.84	1.17	2.47	11
													95	74	6.90	1.07	2.26	11
71	120	92	4.27	2.15	3.52	18	138	101	5.42	1.86	3.03	13						
	97	94	3.76	2.50	4.07	26												
79	86	85	4.93	1.72	3.06	20	93	89	7.01	1.16	2.06	12						
	72	77	4.18	1.84	3.28	25												
Mean.....	88	94	4.37	2.15	3.47	25	99	106	5.97	1.78	2.90	18	102	104	6.79	1.53	2.54	15

TABLE IX

Pressures and Ventricular Work Against Pressure in Dogs with Constriction of the Left Auricle and Ventricle

DOG NUMBER	JUGULAR VEIN MM. Hg		RIGHT AURICLE MEAN MM. Hg		RIGHT VENTRICLE MM. Hg		PULMONARY ARTERY MM. Hg		PULMONARY ARTERY MEAN MM. Hg		PULMONARY "CAPILLARY" MEAN MM. Hg		CARDIAC INDEX L/MIN./M²		RIGHT VENTRICULAR WORK AGAINST PRESSURE KILOGRAM METERS/MIN./M²		LEFT VENTRICULAR WORK AGAINST PRESSURE KILOGRAM METERS/MIN./M²		FEMORAL ARTERY MEAN MM. Hg	
	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper
VA #12	4	3	2		25/0		24/7		14		6		3.65	2.54	0.69		5.76		122	114
32	3	5	0	3	29/0	62/2	29/10	62/28	16	39	9	21	3.61	2.37	0.79	1.16	6.14	3.42	136	127
35	4	3	1	0	26/0	48/0	24/8	47/29	14	34	8	20	3.69	3.01	0.65	1.39	5.22	3.93	112	116
38	3	6	0	4	23/0	72/4	23/7	70/34	12	47	6	17	3.48	1.84	0.57	0.98	5.58	2.63	124	122
39	2	2	0	0	27/0	34/0	27/9	38/19	14	28	7	16	3.44	2.92	0.65	1.11	4.96	3.65	113	108
40	2	9	−2	9	25/1	88/9	25/11	88/36	16	59	8	27	3.56	2.29	0.87	1.56	5.04	2.43	112	105
41	3	5	1	1	26/0	43/1	26/8	45/23	16	33	9	18	3.81	2.78	0.78	1.21	5.49	3.48	115	110
42	4	4	1	4	23/0	61/3	22/6	61/27	12	42	6	19	3.11	2.33	0.47	1.20	4.40	2.95	110	112
51	1	3	−1	0	28/0	39/0	28/7	39/15	13	29	6	14	3.52	2.64	0.67	1.04	5.38	3.59	118	114
52	3	5	1	3	31/0	57/3	30/12	57/29	18	40	10	22	3.04	2.28	0.70	1.15	4.71	3.01	124	119
71	4	5	1	0	25/0	42/0	25/9	38/18	13	23	8	12	3.80	2.75	0.62	0.86	5.12	3.48	107	105
79	4	7	3	6	24/1	69/6	24/10	73/44	17	51	9	23	3.17	2.06	0.60	1.26	4.61	2.52	116	113
Mean.....	3	5	1	3	25/0	56/3	25/9	56/27	15	39	8	20	3.49	2.48	0.67	1.17	5.21	3.19	118	114

Discussion

A volume-elasticity curve for the left ventricle may be plotted in a fashion similar to that for the right ventricle, (see Fig. 12).

In the dogs with chronic pericardial constriction of the left auricle and ventricle one may visualize that the volume-elasticity of these chambers changed, creating a handicap in left ventricular diastolic filling wherein greater filling pressure was essential to return blood to this chamber to maintain cardiac output. An index of this handicap is the level of elevation of left ventricular filling pressure (or approximately pulmonary "capillary" mean pressure) which averaged 20 millimeters of mercury in these dogs.

Venous return to the right ventricle continued at normal filling pressure, since the volume-elasticity of its myocardium and pericardium was unaltered. Systemic (peripheral and central) venous pressures thus remained at control levels.

Left auricular and pulmonary venous pressures, as indicated by pulmonary "capillary" mean pressures, were elevated as a result of an increase in left ventricular resistance in diastole. This was confirmed by direct measurements by arterial cardiac catheterization in several dogs. Right ventricular systolic pressure and pulmonary arterial and "capillary" mean pressures were also elevated. This seems to have been caused by increased left ventricular resistance in diastole and increased pulmonary "arteriolar" resistance coincident with good right ventricular function. Similarly pulmonary "arteriolar" resistance increases have been calculated in patients with mitral stenosis (54, 55) and other cardiac anomalies (56) and have been attributed at least in part to pulmonary vascular changes (56, 57, 58, 59). Increased vascular tone has been hypothesized (54, 55).

As scarring progressed, the cardiac output and stroke volume fell somewhat (less than with constriction of the right side of the heart).

Because of greatly increased pulmonary resistance and resultant pulmonary hypertension and despite reduced cardiac output, right ventricular work against pressure increased markedly.

Although the cardiac output was reduced, systemic resistance increased, supporting systemic arterial pressure. Since systemic arterial pressure remained almost normal, left ventricular work against pressure declined corresponding to the reduction in cardiac output.

In one dog, VA #40, in addition to similar changes in hemodynamics, the right ventricular end diastolic pressure and systemic venous pressure became elevated with the development of hepatomegaly, slight ascites, and peripheral edema.

These changes in hemodynamics were reversible by excision of the constricting pericardial scar over the left side of the heart, showing that myocardial function was good.

RIGHT AURICULAR CONSTRICTION

Chronic pericardial constriction localized to the right auricle was produced in ten dogs. After five to nine months, these dogs had no significant deviation in resting cardiac index, oxygen consumption, arteriovenous difference, or pulmonary or systemic blood pressures. They remained vigorous throughout, and none developed ascites, hepatomegaly, or edema.

Results of pericardiectomy

In a dog, VA #49, with the whole heart chronically constricted, the pericardial scar and plastic cast overlying the right auricular and venae caval regions were excised. There followed no decline in venous pressure or improvement in cardiac output. Ascites persisted. The animal died four and one-half weeks later with anasarca. A second dog, VA #59, with the whole heart chronically constricted had all of its pericardial scar except that covering the right auricle removed. This dog was sacrificed in good health with normal venous pressure after seventeen weeks.

Discussion

Gorlin and Haynes (60) and Gorlin and Gorlin (61) have utilized the hydraulic principles and formulae of fixed orifices or short tubes to calculate the size of stenotic cardiac valves. They have found from cardiac catheterization studies that mitral stenosis must be quite "tight" to cause symptoms on exertion, as Bland and Sweet have pointed out clinically (62). Gorlin states that the mitral valvular area must be reduced from a normal of 4 to 6 square centimeters to about 1.5 square centimeters to cause symptoms on ordinary exertion (61).

If only the right auricular segment of the cardiac tract is constricted, and this segment is considered to be a short tube to which similar hydraulic formulae roughly apply, it may be concluded that a very large reduction in cross sectional area must take place before a significant increase in systemic venous pressure is required to maintain resting blood flow (venous return). Gibbon, Hopkinson, and Churchill demonstrated the validity of the same principle in reference to gradual occlusion of the pulmonary artery. They showed that the pulmonary artery can be obstructed up to 60 per cent of its cross-sectional area without significant effect upon arterial or venous pressures (63).

At autopsy these dogs had extremely thick localized pericardial scarring over the right auricle, but in none of them was the crossed-sectional area of the right auricular lumen narrowed to less than the normal cross-sectional area of the tricuspid valve.

Constriction of the right auricle to the point of obstructing the flow of blood into the right ventricle is accompanied by a higher venous pressure proximal to the obstruction and a lower pressure distal to it. In these dogs with con-

striction of the right auricle there was very little difference in vena caval, right auricular, and right ventricular end-diastolic pressures. In the series of dogs with constriction of the right auricle and ventricle and in a later series with constriction of the whole heart the same was found to be true.

Parsons and Holman were able to produce ascites in dogs by partial ligation of the inferior vena cava to half its outside diameter (11). They were unable to produce ascites by localized pericardial scarring over the right auricle.

It is theoretically possible to have such severe constriction of the venae cavae or right auricle by pericardial scarring that ascites will result. However, this advanced degree of constriction was not accomplished in the present series of experiments and not in those of Parsons and Holman.

Liberation of the right auricle in a dog with constriction of the whole heart caused no improvement in that animal's cardiovascular status. In a second dog with constriction of the whole heart, apparent cure followed removal of all the pericardial scar save that covering the right auricle. As will be noted in the next section, eight animals with constriction of the whole heart exclusive of the right auricle developed ascites. Together, this information indicates that constriction of the auricles must rarely be of primary importance in constrictive pericarditis.

CONSTRICTION OF THE WHOLE HEART EXCLUSIVE OF THE RIGHT AURICLE

Eight of fifteen dogs with intrapericardial casts over the whole heart except the right auricle survived into the phase of chronic constriction. Each had elevation of systemic venous pressure, hepatomegaly, and ascites, as did the dogs with constriction of the right auricle and ventricle. Contrary to the dogs with constriction of the right side of the heart they had pulmonary hypertension. This is similar to dogs with constriction of the left auricle and ventricle previously described and to animals with constriction of the whole heart to be described. Detailed consideration of hemodynamic data obtained from this group of animals will be omitted to avoid duplication of quite similar data obtained from dogs with constriction of the whole heart, which will be reported later.

Discussion

The principal points which are demonstrated by these dogs are (a) the relatively unimportant contribution of constriction of the right auricle, and (b) conversely, the important contribution of constriction of the ventricles to the pathologic physiology of constrictive pericarditis.

GENERALIZED CONSTRICTION OF THE HEART

The sequence of changes following the placement of a plastic cast intrapericardially about the whole heart resembled closely the sequence noted in dogs where the cast was placed locally over the right side of the heart.

There was an acute phase extending about one to two weeks, beginning after the cast was inserted with elevated peripheral and central venous pressures and increased cardiac output, followed by accumulation of edema fluid, and ending usually with a spontaneous diuresis. Davis, et al. (8) who have carried out balance studies in comparable experiments, as previously mentioned, found early sodium and fluid retention which they attributed to an adrenal cortical mechanism.

Electrocardiographic recordings revealed sinus tachycardia and elevated ST segments, indicative of acute pericarditis.

The chronic phase was then entered, in which the dogs stabilized with slight ascites for a variable period (2 to 6 weeks) at moderately elevated systemic venous pressures and approximately normal cardiac indices. Subsequently, jugular, right auricular, and right ventricular filling pressures rose even higher and more prominent ascites accumulated (64). There was a slow decline in cardiac output with an elevation in A-V difference (65). Grossly, these dogs as well as dogs with all the heart constricted except the right auricle were comparable to dogs with constriction of the right side of the heart. However, determination of the pulmonary pressures by catheterization revealed an important difference between dogs which had only the right ventricle involved in the constrictive process and dogs which also had the left ventricle constricted, namely: there was pulmonary hypertension whenever the left ventricle was constricted. Pulmonary hypertension was marked or moderate depending upon the balance of simultaneous constriction of the right and left ventricles.

In the chronic phase electrocardiograms showed low voltage QRS complexes, flattened or inverted T waves, and sinus tachycardia.

Table X outlines cardiac output values in these animals with constriction of the whole heart. The average cardiac index declined from a control of 3.19 to 2.33 liters per minute per square meter of body surface area during the interval of the first six postoperative weeks and thence to 1.75 in later weeks. Arteriovenous difference ascended while oxygen consumption was unaltered.

Table XI summarizes the pressure and ventricular work data. In the chronic phase of constriction the jugular, right auricular, and right ventricular end-diastolic pressures became notably increased, these ascending from control averages of 3, 0, and 0 to averages of 14, 13, and 12 millimeters of mercury respectively. The averages of the pulmonary arterial systolic and diastolic and pulmonary arterial and "capillary" mean pressures rose from control levels of 27/9, 16, and 9 millimeters of mercury to levels of 37/19, 26, and 15 millimeters of mercury in the chronic phase. Femoral arterial mean pressure fell slightly from a preoperative average of 116 millimeters of mercury to 107 millimeters of mercury with chronic constriction of the whole heart.

Average right ventricular work against pressure declined from a value of 0.71 to 0.38 kilogram meter per minute per square meter of body surface area. Left ventricular work against pressure also declined.

TABLE X

Oxygen Consumption, A - V Difference, Cardiac Output Cardiac Index, and Stroke Volume in Dogs with Constriction of the Whole Heart

DOG NUMBER	PREOPERATIVE (CONTROL)						POSTOPERATIVE (<6 WEEKS)						POSTOPERATIVE (> 6 WEEKS)					
	P.	O_2 Cons. cc/min.	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke	P.	O_2 Cons. cc/min.	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke	P.	O_2 Cons. cc/min.	A-V Diff. vol. %	C.O. L/min.	C.I. L/min/M^2	S.V. cc/ stroke
VA #48	92	80	4.93	1.62	3.25	18	112	87	5.90	1.47	2.22	13	129	81	8.56	0.95	1.64	7
49	80	139	7.02	1.98	2.94	25							120	129	10.19	1.27	1.80	11
50	74	116	4.29	2.73	3.32	37	95	135	6.38	2.12	2.60	22						
							108	113	7.96	1.42	1.78	13						
59	64	82	4.86	1.69	3.15	26	92	95	6.88	1.38	2.58	15	105	75	6.93	1.08	2.04	10
	79	76	4.10	1.85	3.43	23												
60	88	72	3.96	1.82	3.09	21							114	60	6.75	0.89	1.49	8
65	95	129	5.50	2.35	3.36	25	108	122	7.57	1.61	2.61	15						
67	102	76	3.67	2.07	3.22	20	134	82	8.49	0.97	1.44	7						
70	96	95	5.36	1.77	2.81	18	103	96	5.85	1.64	2.62	16	144	89	8.61	1.03	1.71	7
	90	89	4.25	2.09	3.34	23												
75	86	128	4.37	2.93	3.48	34	94	142	6.18	2.30	2.73	24	110	132	7.22	1.83	2.18	17
	69	110	4.66	2.36	2.82	35												
	75	124	4.01	3.09	3.68	41												
76	84	65	5.03	1.29	2.71	15	90	75	6.52	1.15	2.40	13	106	64	9.47	0.68	1.42	6
	87	79	4.79	1.65	3.42	19												
Mean.....	84	97	4.72	2.06	3.19	25	104	105	6.86	1.53	2.33	15	118	90	8.25	1.09	1.75	9

P. = Pulse. C.O. = Cardiac Output. S.V. = Stroke Volume. C.I. = Cardiac Index. O_2 Cons. = Oxygen Consumption. A - V Diff. = Arteriovenous Difference.

TABLE XI

Pressures and Ventricular Work Against Pressure in Dogs with Constriction of the Whole Heart

DOG NUMBER	JUGULAR VEIN MM. Hg		RIGHT AURICLE MEAN MM. Hg		RIGHT VENTRICLE MM. Hg		PULMONARY ARTERY MM. Hg		PULMONARY ARTERY MEAN MM. Hg		PULMONARY "CAPILLARY" MEAN MM. Hg		CARDIAC INDEX L/MIN/M²		RIGHT VENTRICLE WORK AGAINST PRESSURE KILOGRAM METERS/MIN./M²		LEFT VENTRICLE WORK AGAINST PRESSURE KILOGRAM METERS/MIN./M²		FEMORAL ARTERY MEAN MM. Hg	
	Pre-oper	Post oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper
VA #48	2	14	−1	13	28/1	37/12	28/9	35/16	15	25	8	15	3.25	1.64	0.71	0.27	4.22	2.20	126	114
49	4	10	1	10	28/0	32/9	24/7	31/12	14	19	7	12	2.94	1.80	0.52	0.22	4.44	2.40	118	110
50	3	13	2	12	30/0	42/10	30/12	42/21	16	30	10	19	3.32	1.78	0.63	0.43	4.80	2.34	116	115
59	3	12	−1	10	24/0	35/10	24/10	35/18	15	23	9	16	3.29	2.04	0.90	0.36	4.37	2.44	106	104
60	2	16	0	15	26/0	29/15	26/8	29/17	13	21	6	14	3.09	1.49	0.55	0.12	4.33	1.70	109	98
65	5	19	−2	19	27/−1	43/18	27/12	43/27	18	36	11	20	3.36	2.61	0.91	0.60	4.71	2.95	114	103
67	4	17	1	16	30/0	36/16	30/10	36/22	17	28	8	18	3.22	1.44	0.70	0.24	4.20	1.11	104	95
70	2	8	0	7	27/0	51/6	26/9	51/30	14	39	8	21	3.08	1.71	0.59	0.74	4.48	2.16	115	115
75	4	11	−1	10	24/−1	34/11	24/6	34/19	15	26	9	17	3.32	2.18	0.90	0.47	5.06	2.58	121	104
76	3	15	1	14	29/0	40/10	29/11	36/12	18	30	10	20	3.06	1.42	0.71	0.31	5.08	1.78	132	112
Mean.....	3	14	0	13	27/0	38/12	27/9	37/20	16	28	9	17	3.19	1.81	0.71	0.38	4.57	2.19	116	107

Average left ventricular resistance in diastole was 8.1, compared with a control average of 2.4, and average pulmonary "arteriolar" resistance was 6.0 in comparison with a 2.1 control. Systemic resistance was elevated, and right ventricular resistance in diastole was greatly increased.

Results of partial pericardiectomies

After seven of the dogs with generalized constrictive pericarditis had survived from four to nine weeks, the scarred pericardium and cast were removed from the right auricle and ventricle in three dogs, from the left auricle and ventricle in two, from the right auricle in one, from the whole heart in one, and from the whole heart exclusive of the right auricle in one dog.

The first dog, VA #50, which had the right auricular and ventricular scar excised, died during surgery from blood loss. The right ventricle was entered inadvertently twice. After partial release the right heart dilated considerably.

In the second and third dogs with generalized constriction of the heart, VA #48 and VA #75, the pericardial scar over the right auricle and ventricle was successfully removed. The dogs then had localized constriction of the left side of the heart. VA #48 lived three and one half weeks and died in pulmonary edema. Systemic venous and right auricular pressures fell from 14 millimeters of mercury to 5 millimeters of mercury in four days. Ascites disappeared in the first week and did not recur. No ascitic fluid was found post mortem. On the sixteenth day following right hemipericardiectomy the pulmonary arterial and "capillary" mean pressures were 32 and 18 millimeters of mercury respectively. This was a further increase of the previously elevated values of 25 and 15, obtained before pericardiectomy. Cardiac index was 1.64 liters per minute per square meter of body surface area before pericardiectomy and 1.95 after. VA #75 survived nineteen days and gave much the same picture with a fall in systemic venous pressure from 11 millimeters of mercury to 6 millimeters of mercury on the day after partial pericardiectomy. Ascites was not detectable by the tenth day. There was gross pulmonary edema on post mortem examination.

VA #65 and VA #67 had excision of the pericardial scar over the left auricle and ventricle. These dogs then had localized constriction of the right side of the heart. Aside from the fact that the pulmonary hypertension was relieved, there was no change in the signs and symptoms due to systemic congestion. After six weeks both animals succumbed but without pulmonary edema. In VA #67 prehemipericardiectomy pulmonary arterial and "capillary" mean pressures were 28 and 18 millimeters of mercury. Following the left hemipericardiectomy these fell to 19 and 13 millimeters of mercury. Cardiac indices before and after surgery were 1.44 and 1.57 liters per minute per square meter of body surface area. In VA #65 pulmonary arterial mean pressures pre- and post-left hemipericardiectomy were 36 and 22 millimeters of mercury respectively.

VA #49 showed no improvement in the month following isolated excision of the right auricular scar and cast.

VA #59 returned to normal cardiovascular hemodynamics subsequent to removal of all the pericardial scar save that covering the right auricle. Jugular venous pressure descended from 12 millimeters of mercury to 5, and the ascites was absorbed. This dog was sacrificed in good health after twelve weeks. Heavy scarring covered only the right auricle.

VA #60 was vastly improved by total pericardial decortication (66) (67). Jugular venous pressure dropped from 16 to 3 millimeters of mercury almost immediately after operation, and pulmonary arterial mean pressure fell from a level of 21 millimeters of mercury to 15.

A ninth dog with generalized constriction, VA #76, died during anesthetic induction before proposed left hemipericardiectomy could be attempted.

Discussion

As previously discussed, volume-elasticity curves (Fig. 12) may be plotted for the right and left ventricles. If the pericardium over both ventricles is thickened so that its modulus of elasticity is increased, to fill the ventricles with a volume of blood adequate to maintain cardiac output requires greater than usual ventricular diastolic filling pressure.

An index of the right ventricular filling handicap is the degree of elevation of right ventricular filling pressure, which averaged 12 millimeters of mercury in these dogs. An index of the left ventricular filling handicap is the level of elevation of the left ventricular filling pressure (or approximately pulmonary "capillary" mean pressure), which averaged 17 millimeters of mercury in those dogs (Table XI).

Apparently homeostatic mechanisms in maintaining cardiac output by maintaining venous return to the right and left ventricles brought about an increase in systemic and pulmonary venous pressures, since both of the latter values are increased.

With the rise in systemic venous pressure and while resting cardiac output was still within control limits, hepatomegaly and ascites developed. With the rise in pulmonary venous pressure rales became auscultable (dogs VA #50, 65, 67, and 70), and in some dogs (VA #50, 65, and 70) pulmonary edema was found at autopsy. Pulmonary pressures were elevated (37, 68, 70, 74), but in most cases they did not rise as high as with isolated constriction of the left side of the heart. It appears that constriction of the right ventricle with limitation of its output has a restricting influence upon the degree of elevation of pressures in the pulmonary circuit in this situation.

As the scarring progressed and compensatory venous return mechanisms became inadequate, the pulse rate was markedly accelerated, and resting cardiac output and stroke volume fell (65).

(Table VII). The average pulmonary "arteriolar" resistance was increased,

though less so than with localized constriction of the left side of the heart and more so than with localized constriction of the right side of the heart. Average right and left ventricular resistances in diastole due to the bilateral pericardial scarring were simultaneously elevated. These resistances were elevated in the

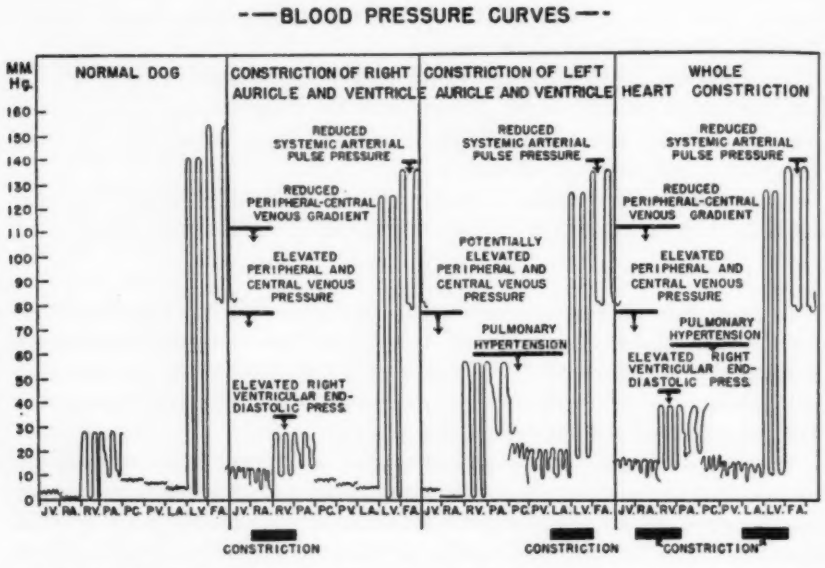

--BLOOD PRESSURE CURVES--
MM Hg.
NORMAL DOG
CONSTRICTION OF RIGHT AURICLE AND VENTRICLE
CONSTRICTION OF LEFT AURICLE AND VENTRICLE
WHOLE HEART CONSTRICTION
REDUCED SYSTEMIC ARTERIAL PULSE PRESSURE
REDUCED PERIPHERAL-CENTRAL VENOUS GRADIENT
ELEVATED PERIPHERAL AND CENTRAL VENOUS PRESSURE
POTENTIALLY ELEVATED PERIPHERAL AND CENTRAL VENOUS PRESSURE
PULMONARY HYPERTENSION
ELEVATED RIGHT VENTRICULAR END-DIASTOLIC PRESS.
JV. RA. RV. PA. PC. PV. LA. LV. FA.
CONSTRICTION

FIG. 19. These schematic blood pressure curves illustrate the average pressure values obtained from all the dogs before pericardial constriction and from the various series of dogs after chronic pericardial constriction of the right auricle and ventricle or left auricle and ventricle or whole heart. The fundamental change occurred in the ventricular end-disatolic pressure within the ventricle which had been constricted. If the right ventricle was constricted, elevated systemic venous pressure was observed, presumably to compensate for the elevation in right ventricular end-diastolic pressure and thus to assist in return of blood to the right ventricle. If the left ventricle was constricted, elevated pulmonary pressures were observed, presumably to compensate for elevation of left ventricular end-disatolic pressure and thus to assist in return of blood to the left ventricle. If the right ventricular function was insufficient in the dogs with constriction of the left auricle and ventricle, venous pressure rose on the systemic side of the circulation as well. When the blood pressure gradient between the periphery and a ventricle, either right or left, could not be maintained by compensatory mechanisms, cardiac output fell.

same range as they were individually with isolated right and left heart constrictions. Systemic arterial mean pressure was reduced less than the reduction in cardiac output would indicate, since systemic resistance increased.

Right ventricular work against pressure declined, but not as markedly as

with localized constriction of the right auricle and ventricle. This was true because pulmonary arterial mean pressure was greater with the increased pulmonary resistance following constriction of the left side of the heart. Left ventricular work against pressure decreased, as it did with localized constriction of either the right or left side of the heart. The cause of this was reduced cardiac output while arterial pressure remained near control levels.

In these dogs with generalized pericardial constriction, by removing the pericardial scar over the right side of the heart alone or over the left side alone diametrically opposite hemodynamic situations were developed which were analogous to isolated constriction of the left side of the heart or of the right side of the heart respectively. By removing the scar over both sides of the heart hemodynamic values reverted toward normal (66) (67). By excision of the right auricular scar in animals with generalized pericardial constriction no alteration in hemodynamics was produced. By excision of all the scar but that over the right auricle hemodynamics approaching normal were effected.

These findings together would make it appear that the crux of the pathologic physiology of constrictive pericarditis is situated at the ventricles.

Figure 19 is a schematic comparison of the blood pressure relationships in the normal dog and in dogs with various types of pericardial constriction, based on the average data for the various groups of dogs. The circulatory schema is adapted from Starling (69). This illustrates how the effects of constriction of the left and right sides of the heart are combined in generalized pericardial constriction. Note that right ventricular end-diastolic pressure is elevated if the right ventricle is constricted and that left ventricular end-diastolic pressure is elevated if the left ventricle is constricted.

SUMMARY

1. Chronic constrictive pericarditis was produced in dogs by placing plastic casts within the pericardium. It was possible to localize the pericarditis by placing the casts within pericardial pockets, outlined by suturing the pericardium to the myocardium wherever desired.

2. Four series of dogs were thus prepared with constrictive pericarditis localized to (a) the right auricle and ventricle, (b) the left auricle and ventricle, (c) the right auricle, and (d) the whole heart except the right auricle. A fifth series had generalized constrictive pericarditis.

3. Data concerning the cardiovascular hemodynamics in dogs with these various pericardial constrictions were presented.

4. The results of whole or partial excision of the pericardial scars in these dogs were described.

5. Animals with pericardial constriction of one or both ventricles had a fall in cardiac output and stroke volume.

6. Dogs with pericardial constriction involving the right ventricle alone or the right ventricle in combination with constrictions elsewhere developed elevated systemic venous (peripheral and central) pressure, hepatomegaly, ascites, peripheral edema, and hydrothorax. These changes were reversed with removal of the right ventricular pericardial scar.

7. Dogs with pericardial constriction involving the left ventricle alone or left ventricle in combination with constrictions elsewhere developed rales, accentuated second pulmonic sounds, and pulmonary hypertension. Where the constriction was localized to the left side of the heart alone, pulmonary edema was much more prone to develop. Also, when the constriction was localized to the left size of the heart alone, systemic venous pressure remained normal as long as right ventricular function was sufficient. These changes were reversed when the left ventricular pericardial scar was removed.

8. Dogs with isolated pericardial constriction of the right auricle showed no changes in hemodynamics or physical signs. Where the right auricular scar was excised in dogs with generalized constriction, no improvement in hemodynamics resulted. In dogs with generalized pericardial constriction when the scar was removed from all regions except that over the right auricle, there was marked improvement, as if a total pericardiectomy had been done.

9. Release of the scar over the right side of the heart in two dogs with generalized pericardial constriction produced a situation similar to isolated constriction of the left side of the heart. Ascites disappeared, but these animals died in pulmonary edema.

10. When both ventricles were constricted simultaneously, a combination of systemic and pulmonary vascular congestion resulted with both systemic and pulmonary venous hypertension.

11. A concept of the pathologic physiology of constrictive pericarditis is advanced (a) in which constriction of either or both ventricles is held to be of primary importance, constriction of the auricles rarely if ever being of primary importance, and (b) in which an explanation for the mechanical handicap in ventricular diastolic filling is postulated on the basis of alteration of ventricular volume-elasticity characteristics by the pericardial scar. (Post mortem ventricular volume-elasticity curves for the dog before and after pericardial constriction were presented.) Myocardial factors other than the mechanical handicap of pericardial constriction are not ruled out.

12. Application of this concept to the surgical correction of constrictive pericarditis suggests that total excision of the pericardial scar is to be desired, but that liberation of both ventricles is essential.

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THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) ADMINISTRATION ON SKIN, CONJUNCTIVAL, AND NASAL MUCOUS MEMBRANE REACTIVITY TO HISTAMINE AND ANTIGENS IN MAN[1]

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The resemblance between the pharmacologic effects of histamine and some of the manifestations of allergic and anaphylactic reactions, and the presence of histamine in bound form in normal tissues, has led to the suggestion that the reaction between antigen and antibody may be followed by the release of histamine or a histamine-like substance (2, 3). The role that such a substance may play in allergic diseases, and in diseases of mesenchymal tissue which may be due to hypersensitivity, is not known (4). Nevertheless, the suggestion has been made that the beneficial influence of adrenal cortical and adrenocorticotropic hormones in these diseases may be mediated by reduction in sensitivity to (5) or availability of (6–8) histamine. This suggestion is largely based on the observations that removal of the adrenal glands or hypophysis of the rat results in an increase in susceptibility to anaphylactic shock, accompanied by an increase in susceptibility to histamine poisoning (5), a decrease in the ability of excised tissues to inactivate histamine (9), and an increase in the release of histamine following various stimuli (10), and that restoration of adrenal cortical hormone results in opposite changes. In species other than the rat these relationships have not been as evident, but parallelism has been noted between susceptibility to anaphylactic shock and to histamine poisoning in some species, such as the guinea pig, where it is high, and the rat, where it is low (11).

In the report to be presented observations have been made on the effect of ACTH administration, in doses sufficient to induce a clinical remission in patients with allergic or "hypersensitive" disease, on dermal, conjunctival, and nasal mucous membrane reactivity to histamine and to various antigens. The skin was not the site of disease in these patients, though it did respond to the injection of suitable antigens. The conjunctivae and nasal mucous membranes were the site of allergic disease, in most instances hay fever, though not visibly altered at the time reactivity was determined. Studies have also been carried out on the effect of ACTH on the general vascular reactivity to histamine,

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and on the ability of the skin and adjacent tissues to liberate histamine-like substance after the administration of d-tubocurarine. This compound is one of several which produce histamine-like effects after intracutaneous or intra-arterial injection, attributable to the release of histamine-like substance from the tissues (12). Observations have also been made on the effect of ACTH administration on the serum concentration of skin-sensitizing antibody.

METHODS

Histamine, d-tubocurarine, and inhalant and bacterial antigens were injected into the skin of patients with allergic or "hypersensitive" disease, and histamine and inhalant antigens instilled into the conjunctivae and nasal mucous membranes of patients with allergic disease, before, during, and after the administration of ACTH (Table I). The tests were repeated on one to three occasions before, during ACTH (on or about the seventh day), and after ACTH (on or about the eleventh day). The hormone was administered intramuscularly to most patients, at six hour intervals, in average daily dose of 87 mg. for 10 days. Five of the patients in whom dermal reactivity to histamine and d-tubocurarine was studied received ACTH intravenously, by slow infusion, in average daily dose of 40 mg. At the time the tests were repeated during and after ACTH administration a clinical remission had been induced in every patient. Observations were made on the effect of ACTH on the response of each tissue to the lowest ("threshold") concentration of test substance that produced a reaction prior to ACTH. The threshold concentration was determined before, during, and after ACTH by the administration of concentrations graded in multiples of two to ten.

Reactivity of skin: One twentieth of a milliliter of graded concentrations of histamine phosphate and d-tubocurarine chloride (Squibb), and one-fortieth of a milliliter of graded concentrations of inhalant and bacterial antigens in normal saline were injected intradermally. The prompt reactivity of the skin to these substances was determined by measuring the wheal and flare that were present fifteen minutes after injection, and the delayed reactivity to antigens by the erythema, edema and induration present twenty-four hours after injection.

Reactivity of conjunctivae: One twentieth of a milliliter of graded concentrations of histamine phosphate and inhalant antigens in normal saline was instilled into opposite conjunctivae of patients with hay fever and extrinsic asthma associated with conjunctival sensitivity at a time when conjunctival injection was minimal or absent. Increasing concentrations were administered at fifteen minute intervals until suffusion of the bulbar and palpebral conjunctivae ensued, usually accompanied by itching and burning.

Reactivity of nasal mucous membranes: This could be studied in only a few patients with hay fever because of the presence of persistent symptoms in most patients prior to ACTH administration. In four patients in whom symptoms were minimal or absent on the day the tests were begun, graded concentrations of histamine phosphate and ragweed in normal saline were administered on separate days by five successive nasal insufflations from an atomizer. In these patients, and in one other patient with hay fever, nasal symptoms could also be induced by conjunctival instillation of ragweed extract. Increasing concentrations of histamine or ragweed were administered at fifteen minute intervals until stuffiness, sneezing, and rhinorrhea ensued.

Antigens administered (Table I): The particular antigens that were administered were those which were presumed to be concerned with the allergic disease in each patient. Nine patients with hay fever were given intradermal, conjunctival, and in four instances intra-

TABLE I

Range of Concentration of Test Substances Administered, and Patients Studied

SUBSTANCE ADMINISTERED AND ROUTE	RANGE OF CONC. (MG./ML. OR MG./ML. PN)**		PATIENTS							
	Low	High	Hay Fever	Extrinsic Asthma	Intrinsic Asthma	Lupus Erythematosus	Rheumatoid Arthritis	Nasal Polyps	Chorioretinitis	Total
Intradermal										
Histamine	10^{-5}	10^{-2}	5	4	4	2	1	1	1	18
d-Tubocurarine	3×10^{-5}	3		4	5	4	1	1	1	16
Inhalant Antigens*			8	4						12
Bacterial Antigens	2×10^{-4}	2×10^{-1}			17	1				18
Inhalant Antigens after passive transfer of serum†			3		3					6
I. M. Histamine	10^{-1}	3×10^{-1}		4	1					5
I. A. d-Tubocurarine	3.7	6					1	1	1	3
Conjunctival (or Intranasal)										
Histamine	10^{-2}	5×10^{-1}	8 (2)	4						12 (2)
Inhalant Antigens‡			9 (4)	3						12 (4)
* *Intradermal Inhalant Antigens*										
Ragweed	2.5×10^{-5}	2.5×10^{-3}	8	1						
Fungi	4×10^{-6}	4×10^{-3}		2						
Dust	4×10^{-5}	4×10^{-3}		1						
† *Intradermal Inhalant Antigens after passive transfer of serum*										
Ragweed	2.5×10^{-7}	2.5×10^{-3}	3		2					
Orris Root	0.7×10^{-4}	0.7×10^{-1}			1					
Dust	6×10^{-5}	1.2×10^{-1}			2					
‡ *Conjunctival Inhalant Antigens*										
Ragweed (also Intranasal)	2.5×10^{-5}	2.5×10^{-1}	9 (4)	1						
Fungi	4×10^{-4}	4×10^{-1}		1						
Dust	1×10^{-1}	1		1						

** The concentration of antigens is recorded as mg. protein N/ml.

nasal test doses of extract of ragweed pollen, since the seasonal incidence of their symptoms was compatible with this pollen being the antigenic agent in their illness, and since conjunctival or nasal instillation of the extract produced marked conjunctival injection and nasal congestion. Four patients with extrinsic asthma were given intradermal and con-

junctival test doses of extract of ragweed pollen, mixed fungi, or mixed dusts, since their clinical history was compatible with extrinsic asthma in which these antigens were an important factor. In addition, two patients who received mixed fungi and one who received dusts had attacks simulating clinical asthma following inhalation of these antigens. All four patients with extrinsic asthma had conjunctival suffusion after local instillation of antigen.

The effect of the conjunctival and intranasal instillation of histamine was observed in these same patients with hay fever and extrinsic asthma. The effect of intradermally administered bacterial antigens was studied in 17 patients with intrinsic asthma, and one with lupus erythematosus.

General vascular reactivity to histamine: Graded doses of histamine phosphate were administered intramuscularly to five patients with bronchial asthma (four extrinsic and one intrinsic) until generalized effects of histamine were noted, including flushing, warmth, and headache. The influence of ACTH was assessed by observation of these effects, and by measurement of skin temperature of the extremities in two of the patients.

Local and general reactivity to histamine-like substance released following intra-arterial injection of d-tubocurarine: d-Tubocurarine chloride was injected into the brachial artery of three patients, in a manner previously described (12). The local histamine-like effects which promptly followed the injection were measured by the increase in skin temperature and volume of the injected extremity, and by the degree of local redness, edema, and wheal formation that occurred. The systemic histamine-like effects which followed the release of a tourniquet applied proximal to the site of injection were measured by the increase in skin temperature of the remaining extremities, and by the increase in secretion of gastric acid that occurred. The weakness of the injected extremity produced by d-tubocurarine was recorded by means of a hand dynamometer. The influence of ACTH on each of these effects was determined.

Concentration of skin-sensitizing antibody in the serum as determined by passive transfer: One-tenth of a milliliter of graded concentrations of the serum of eight patients known to be skin-sensitive to inhalant antigens was administered intradermally in several sites to eight normal subjects who were not skin sensitive. Three one-hundredths of a milliliter of a constant concentration of antigen (Table I) was injected into each site 24 hours later and the threshold (lowest) concentration of serum required to produce a prompt wheal and flare determined. This varied from 2×10^{-5} to 10^{-2} ml. of serum per ml. The threshold concentration was redetermined on the fourth and ninth days of administration of ACTH to the patients, and on the fourth and fourteenth days after cessation of ACTH.

RESULTS

Effect of ACTH on Reactivity of Skin and Adjacent Blood Vessels to Histamine

Prompt reactivity of skin to histamine and d-tubocurarine (Table II): The administration of ACTH had no significant effect on the reactivity of the skin to a constant concentration of these substances, or on the threshold concentration of each substance required to produce a reaction. There was also no significant change after cessation of ACTH.

General vascular reactivity to histamine: ACTH had no appreciable influence on the generalized flushing, increase in digital skin temperature (4 to 8° C), and subjective warmth and headache that followed the intramuscular injection of 0.1 to 0.3 mg. of histamine. There was likewise no change in these effects of histamine after cessation of ACTH.

TABLE II

Effect of ACTH Administration on Skin, Conjunctival, and Nasal Mucous Membrane Reactivity, as Reflected by the Number of Patients Whose Reactivity was Altered to a Constant, Initially Threshold Concentration of each Substance (C) and the Number in Whom the Threshold Concentration was Changed (T)

TABLE II

Effect of ACTH Administration on Skin, Conjunctival, and Nasal Mucous Membrane Reactivity, as Reflected by the Number of Patients Whose Reactivity was Altered to a Constant, Initially Threshold Concentration of each Substance (C) and the Number in Whom the Threshold Concentration was Changed (T)

The average change in threshold concentration is recorded in parentheses after the number of patients. The reactivity during ACTH is compared with that prior to ACTH, while the reactivity after ACTH is compared with that during ACTH. The concentration of antigens is recorded as mg. protein N/ml.

The average dermal reaction to the threshold concentration of each substance prior to ACTH was 0.8 cm. (wheal) × 2.3 cm. (flare). When a change in the dermal reaction to the initially threshold concentration (C) occurred during ACTH, the average increase or decrease was 0.5 × 1.6 cm. Decrease in the conjunctival or nasal reaction to constant concentrations consisted of disappearance of the reaction, and increase after ACTH by return of the reaction.

SUBSTANCE ADMINISTERED	THRESHOLD CONC. BEFORE ACTH (MG./ML.) AVG.	C OR T	TISSUE	TIME OF REACTION	REACTIVITY DURING ACTH			REACTIVITY AFTER ACTH		
					Unchanged	Decreased	Increased	Unchanged	Decreased	Increased
					(No. of Patients)			(No. of Patients)		
Histamine	2.1×10^{-3}	C	Skin	Prompt	13	2	3	15	1	2
Histamine	2.1×10^{-3}	T	Skin	Prompt	7	1 (10×)	6 (10×)	10	0	4 (10×)
d-Tubocurarine	2.0×10^{-3}	C	Skin	Prompt	13	1	2	14	1	0
d-Tubocurarine	2.0×10^{-3}	T	Skin	Prompt	8	2 (10×)	0	8	1	0
Inhalant antigens	3.3×10^{-4} (PN)	C	Skin	Prompt	6	4	2	9	1	2
Inhalant antigens	3.3×10^{-4} (PN)	T	Skin	Prompt	4	4 (10×)	4 (10×)	6	3 (10×)	3 (10×)
Bacterial antigens	8.2×10^{-3} (PN)	C	Skin	Prompt	12	5	0	8	1	4
Bacterial antigens	8.2×10^{-3} (PN)	T	Skin	Prompt	4	1 (5×)	0	2	0	1 (5×)
Bacterial antigens	1.2×10^{-1} (PN)	C	Skin	Delayed	2	16	0	3	0	11
Bacterial antigens	1.2×10^{-1} (PN)	T	Skin	Delayed	1	6 (25×)	0	0	0	3 (25×)
Histamine	2.0×10^{-1}	C	Conjunctivae	Prompt	8	4	0	9	1	3
Histamine	2.0×10^{-1}	T	Conjunctivae	Prompt	7	4 (4×)	1 (2×)	5	2 (2×)	5 (3×)
Inhalant antigens	1.1×10^{-3} (PN)	C	Conjunctivae	Prompt	5	7	0	9	2	1
Inhalant antigens	1.1×10^{-3} (PN)	T	Conjunctivae	Prompt	4	7 (9×)	1 (2×)	8	1 (4×)	3 (18×)
Histamine	0.5	C	Nasal M.M.	Prompt	0	2	0	1	1	0
Inhalant antigens	2.5×10^{-3} (PN)	C	Nasal M.M.	Prompt	1	4	0	2	2	1
Inhalant antigens	2.5×10^{-3} (PN)	T	Nasal M.M.	Prompt	1	4 (31×)	0	2	2 (10×)	1 (10×)

Local and general reactivity to histamine-like substance released following intra-arterial injection of d-tubocurarine: ACTH had no appreciable influence on the histamine-like effects that appeared in the injected extremity (skin temperature rise, redness, edema, wheals) and elsewhere (skin temperature rise, increased secretion of gastric acid). ACTH also had no effect on the degree or duration of weakness of the injected extremity produced by d-tubocurarine.

Effect of ACTH on Reactivity of Skin to Antigens (Table II)

Prompt reactivity of skin to inhalant and bacterial antigens: ACTH had no appreciable effect on the *prompt* reactivity of the skin to these substances in the majority of patients studied. In 4 out of 12, and 5 out of 17 patients there was a decrease in reactivity to a constant concentration of inhalant and bacterial antigens during ACTH, and in three of these patients this concentration produced no wheal or flare during ACTH. In two patients there was an increase in prompt reactivity to inhalant antigens during ACTH. The average size of the wheal and flare produced in all the patients by constant concentrations of these substances was not appreciably changed during or after ACTH. The threshold concentration of inhalant antigens was unchanged, decreased, and increased in approximately equal numbers of patients during ACTH, and the average value was not appreciably changed. The threshold concentration of bacterial antigens was unchanged in four patients and increased five fold in one patient during ACTH.

Delayed reactivity of skin to antigens: During the administration of ACTH there was a moderate reduction in the *delayed* reactivity of the skin to this group of substances in almost every patient. The erythema produced by a constant concentration of bacterial antigen was reduced in 16 of 18 patients during ACTH to about one fourth the original size. The edema and induration that accompanied the erythema could not be accurately measured, but appeared to be proportionately reduced. In 6 of the 18 patients the original threshold concentration produced no appreciable erythema, edema, or induration during ACTH. The threshold concentration required to produce a reaction was increased an average of 25 fold in 6 of 7 patients during ACTH. Following cessation of ACTH there was a return to or near the original reactivity in 11 of 14 patients in whom this had been diminished.

In only one patient did the intradermal injection of an inhalant antigen (ragweed) produce a delayed reaction. During the administration of ACTH this was markedly reduced, while the prompt reaction to this antigen was unaltered.

Effect of cortisone on prompt and delayed reactivity of the skin to bacterial antigens: This was studied in four patients with intrinsic bronchial asthma, before, during, and after the intramuscular administration of an average of 110 mg. of cortisone daily for 8 days. The skin tests were repeated on or about the

fifth day of cortisone administration, and six days after the cessation of cortisone. There was no significant change in the *prompt* reactivity of the skin to a constant concentration of antigen. The *delayed* reactivity, on the other hand, was moderately reduced during cortisone administration, the erythema produced by a constant concentration of antigen being reduced to about one half the original size. The delayed reactivity returned to its original level following cessation of cortisone. These effects of cortisone administration were similar to those of ACTH, although the reduction in delayed reactivity during cortisone, in the doses that were administered, was not quite as great in this small group of patients as that observed during ACTH.

Effect of ACTH on Reactivity of Conjunctivae and Nasal Mucous Membranes (Table II)

Reactivity of conjunctivae to histamine: In 8 out of 12 patients with hay fever or extrinsic asthma ACTH did not influence this reactivity, as indicated by the response to a constant concentration or by determination of the threshold concentration. In 4 patients reactivity was diminished to some extent during ACTH. In these patients the average threshold concentration required to produce a reaction was four times higher during ACTH. In one other patient there was some increase in reactivity, the threshold concentration being 50 per cent less than before ACTH. Following cessation of ACTH, a minority of the patients showed some increase in reactivity, compared to that during hormone administration, and a smaller number a decrease.

Reactivity of conjunctivae to inhalant antigens: In 7 out of 12 patients there was a moderate decrease in reactivity. In these patients the average threshold concentration required to produce a reaction was nine times higher during ACTH. In one other patient there was some increase in reactivity, the threshold concentration being 50 per cent less than before ACTH. The decrease in conjunctival reactivity to inhalant antigens was greater than to histamine, and usually appeared at an earlier time during hormone administration. The patients whose reactivity to inhalant antigens was unchanged during ACTH had as complete a remission of their hay fever or extrinsic asthma as did those whose reactivity was diminished. Following cessation of ACTH, the reactivity to inhalant antigens returned to or near the original level in three out of seven patients.

Reactivity of nasal mucous membranes to histamine: In each of two patients nasal reactivity to the intranasal or conjunctival instillation of 0.5 mg./ml. of histamine was abolished during ACTH. Following cessation of hormone administration, this concentration of histamine elicited a reaction in one of the two patients.

Reactivity of nasal mucous membranes to inhalant antigens: In three of four

patients there was a marked decrease in nasal reactivity to intranasal or conjunctival ragweed during ACTH, as manifested by a 31 fold average increase in the threshold concentration required to induce symptoms. In the other patient there was no change, even though the symptoms of hay fever disappeared. Following cessation of ACTH, nasal reactivity to ragweed increased in this patient. In the other three patients, reactivity decreased further in two after cessation of ACTH, and did not change in the third.

Effect of ACTH and Cortisone on Serum Concentration of Skin-Sensitizing Antibody

In 6 of 8 patients, ACTH had no effect on the serum concentration of skin-sensitizing antibody, as determined by passive transfer tests. In two patients this concentration increased, by two and twenty fold. Following cessation of ACTH, the serum antibody concentration remained unchanged in 3 of 6 patients, increased two fold in two patients, and ten fold in one. The effect of cortisone administration (100 mg. a day intramuscularly for eight days) was studied in one patient. An initial ten fold decrease in antibody concentration was observed on the third day of cortisone, but on the sixth day the concentration was the same as prior to cortisone.

DISCUSSION

The effect on tissue reactivity of the doses of ACTH that were administered appeared to depend upon the nature and probably the state of the tissue, the nature of the irritant substance, and the type of tissue reaction.

Reactivity of Skin

The observations on dermal reactivity, which were summarized in an earlier report (13), are in agreement with the observations of others that ACTH does not affect reactivity of the skin to histamine or prompt reactivity to inhalant antigens (7, 14, 15), but does diminish delayed reactivity to bacterial antigens (16). They also indicate that even a high level of adrenal cortical stimulation by intravenous ACTH does not alter the ability of skin and other tissues of the upper extremity to release histamine-like substance (following d-tubocurarine) or to respond to this substance or to histamine. These observations make it appear unlikely that the therapeutic effect of ACTH in allergic and "hypersensitive" diseases is mediated or accompanied by a general reduction in the reactivity to, or availability of histamine. The failure of antihistamine compounds to influence many allergic and "hypersensitive" diseases which are favorably affected by ACTH and cortisone is additional evidence against such mediation. It is also of interest that the susceptibility of guinea pigs to the bronchoconstrictor and lethal effects of histamine has been reported to be unaltered by ACTH (17, 18), and that the release of histamine during anaphylaxis in the dog (19), or from sensitized red blood cells following exposure to

antigen *in vitro* (20), has been reported to be unaffected by adrenal cortical extracts and cortisone.

It seems likely that the greater inhibitory effect of ACTH (and of cortisone) on the delayed than on the prompt skin reaction to antigens may be due to qualitative differences in the irritant substances responsible for these reactions, or in the tissue response to these substances. It is well known that the properties of the late intradermal reaction to antigens differ from those of the prompt reaction. The late ("tuberculin type") reaction is the result of both vascular and extravascular cellular changes, while the prompt ("anaphylactic or pollen type") reaction is predominantly vascular (21). The late reaction is not inhibited by antihistamine compounds, in contrast to the prompt reaction (22), which has been more readily related to the release of histamine-like substance. However, the possibility cannot be excluded that quantitative differences in the concentration of irritant substances responsible for these reactions, or in the rate of the reactions, may play a part in determining the degree of inhibiting effect of ACTH. Further study of differences between the prompt and delayed reactions to antigens may help to elucidate the mechanism by which ACTH reduces the inflammatory response to various stimuli.

The skin was not the site of allergic disease in the patients in whom dermal reactivity was studied, though it did respond to the injection of suitable antigens. Numerous clinical observations have shown that, when the skin is the site of allergic disease due to drugs, foreign proteins, or cold, the administration of ACTH or cortisone may ameliorate the cutaneous manifestations, which are often of the prompt, "anaphylactic" type, and may diminish the response to antigen or to cold (23). While these observations have involved different antigens than were employed in the studies that have been described, and in most instances different routes of exposure, they do suggest that ACTH or cortisone may diminish prompt dermal reactivity to antigens more readily when the skin is altered by allergic disease than when it is not so altered.

Reactivity of Conjunctivae and Nasal Mucous Membranes

It is not clear why reactivity of the conjunctivae and nasal mucous membranes to inhalant antigen was not demonstrated to be reduced during ACTH in all the patients with hay fever, since there was a remission of clinical symptoms in all of them at a time when the pollen count was high. Other observers have reported even less frequent diminution in the reactivity of these tissues to antigens during adrenal cortical stimulation (14). It is possible that these tissues may not be entirely suitable for the quantitative measurement of reactivity of allergic tissue, the conjunctivae because of variable involvement by allergic disease such as hay fever, and the nasal mucous membranes because of difficulty in evaluating response to threshold concentrations of irritant substances. Improvement in the technique of determining the lowest concentra-

tion of irritant substance required to produce a reaction, and the administration of larger doses of hormone, may result in more clear cut delineation of the effects of adrenal cortical stimulation. Previous observations on the effect of ACTH on the reactivity to inhalant antigens of another allergic tissue, the bronchial tree of patients with extrinsic asthma (1), are of interest in this regard. ACTH administration was followed by reduced reactivity to inhaled specific antigens, with the degree and duration of this effect being, in general, greater when the threshold concentration of inhaled antigen was low and when the dose of ACTH was high. These observations indicate that the quantitative relationship between the concentration of reacting substance and the degree of the antagonizing effect of ACTH must be taken into account, and that lesser changes in reactivity may be undetected if the concentration of reacting substance is high, or the dose of ACTH low, or the technique of measuring reactivity not sufficiently precise. It may be significant that the original threshold concentration of inhalant antigen or histamine required to elicit conjunctival inflammation in the patients in whom inhibition of reactivity by ACTH was noted was, on the average, less than half that in the patients in whom inhibition was not noted.

The inhibition by ACTH of the prompt reactivity of allergic tissues (conjunctivae, nasal mucous membranes, and bronchial tree) to inhalant antigens, and in some instances to histamine, was in contrast to the lack of appreciable effect of this hormone on the prompt reactivity of the skin to inhalant antigens and histamine, or on the general vascular response to histamine. This difference may be related to the allergic state of the former tissues.

The reduction by ACTH of conjunctival and nasal mucous membrane reactivity to histamine was, in general, less frequent, less marked, and slower in onset than to antigens. Similar observations were made in the studies on bronchial reactivity of patients with extrinsic asthma (1). Since clinical improvement of hay fever and extrinsic asthma, as well as reduced reactivity to antigens, occurred more frequently, to a greater degree, and earlier in the course of ACTH administration than did reduced reactivity to histamine, it seems unlikely that the former were dependent on the latter. The reactivity of allergic tissues to histamine is, in general, greater than that of normal tissues. It is possible that this may not be a specific phenomenon, but rather an illustration of increased reactivity of allergic tissues to many irritant substances. It remains for future study to determine whether or not the variable reduction induced by ACTH in reactivity of allergic tissues to histamine, and even to specific antigens, may be a reflection of a general reduction in reactivity of these tissues to a variety of stimuli.

SUMMARY

1. The administration of ACTH to patients with allergic disease or with disease of mesenchymal tissue believed to be related to hypersensitivity, in

doses sufficient to induce clinical remission, had no effect on the dermal or general vascular reactivity to histamine, on the release of histamine-like substance after intradermal or intra-arterial injection of d-tubocurarine, or on the dermal, general vascular, and gastric secretory reactivity to this substance. These findings suggest that the therapeutic effect of ACTH in allergic and "hypersensitive" disease is not mediated or accompanied by a general reduction in reactivity to histamine, or in the availability of such histamine-like substance as is released by d-tubocurarine.

2. ACTH, in the doses that were administered, had no appreciable effect on the prompt (vascular, histamine-like) reactivity to inhalant antigens, a slight inhibitory effect on the prompt reactivity to bacterial antigens in a minority of patients, and a moderate inhibitory effect on the delayed (vascular and extravascular) reactivity to bacterial antigens in almost every patient.

3. The reactivity of the conjunctivae of patients with hay fever or extrinsic asthma to histamine was reduced in a minority of patients during ACTH, and the reactivity of the nasal mucous membranes was reduced in each of two patients. The prompt reactivity of these tissues to specific inhalant antigens was reduced in most, but not all patients during ACTH. The greater frequency and degree, and earlier onset, of reduced reactivity to antigens and of clinical improvement indicate that these are probably not dependent on reduced reactivity to histamine.

4. It appears likely that ACTH may diminish the prompt reactivity to antigens or histamine of tissues that are altered by allergic disease more readily than tissues that are not so altered.

5. The serum concentration of skin-sensitizing antibody was not significantly affected by ACTH or cortisone administration.

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A METHOD FOR THE DETERMINATION OF ANTIBACTERIAL POTENCY OF SERUM DURING THERAPY OF ACUTE INFECTIONS

A Preliminary Report

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As the list of available antibiotics becomes longer and longer an increasing burden is placed on a clinical bacteriological laboratory to keep pace with this trend. The laboratory is supposed to be able to give the clinician a reliable answer when asked what antibiotic or antibiotics he should use against the infection under consideration. The "paper-disk" technique of studying bacterial cultures for their sensitivity to several antibiotics is a quick method, and may be adequate as a guide in the treatment of most infections. A more accurate estimate of sensitivity may be obtained from the "tube-dilution" test which is another standard laboratory procedure. However, in severe and complicated infections there is a tendency now to employ multiple antibiotic and chemotherapeutic agents in hopes of being able to suppress the infecting microorganisms by a summation of antibacterial effects. Neither of the above tests, in which single cultures and single antibiotics are employed, can be expected to give us the desired information in such infections, and we need a more direct method to help us know how efficiently the patients' own serum, with whatever antibacterial agent it contains, is able to control the infecting bacteria. This becomes all the more important in view of the reports appearing at the present time showing that some agents act synergistically, others by summation of their effects and that others are actually antagonistic (1, 2, 3, 4, 5, 6, 10, 11, 12, 15, 16). These reports will not be reviewed in detail, but the experiments of Jawetz and co-workers are of particular interest in this regard for these workers have shown—both *in vitro* and in experimental infections—that there is definite antagonism between chloramphenicol and penicillin and to a less extent between aureomycin or terramycin and penicillin. This antagonistic effect is dependent to some extent on the size of the penicillin dosage, for it can be abolished by excesses of penicillin; and also on the timing of the injections, because if the penicillin is given first and then allowed to initiate its antibacterial effect, its action is not inhibited by chloramphenicol. These facts make one wonder whether or not the experimental finding of such antagonism between antibiotics has important clinical implications, as so much would seem to depend on the size and timing of the dose of penicillin.

The plan of the present study was to try to determine the bactericidal and

bacteriostatic potency of patients' blood sera against the infecting organisms in cases of severe or complicated infections, and particularly in those in which more than one antibiotic was being employed. A test similar to this in most respects was reported by Schlichter (13) in a series of patients with subacute bacterial endocarditis and other infections while under therapy with penicillin. He felt that it offered a good guide in that type of therapy.

METHODS

The first specimen of blood is obtained before therapy if possible, in order to have a control or base-line reading. Other specimens are taken at various periods during the course of the infection, and at the same time a note made of the types and amounts of drugs being given and of the clinical condition of the patient. Approximately 5 cc. of blood is obtained aseptically and put into a sterile Wassermann tube. This is allowed to clot; it is then centrifuged, the serum removed and usually tested at that time. Sometimes the serum is put in a freezer at −16° C., and tested a day or so later—without any apparent loss in potency, though more data are necessary before we can be sure of that. Serial two-fold dilutions are made in sterile Wassermann tubes—using an appropriate culture medium—in either 0.5 cc. or 1 cc. amounts. The first tube contains the full-strength serum, and the number of tubes used depends on the degree of inhibition or killing expected to occur. This can often be predicted to some extent by the type of therapy and the bacteria under consideration. In most cases six to ten tubes are adequate but occasionally when large doses of penicillin are being used against an organism expected to be very sensitive, the titration is carried out farther. Dilutions are made of fresh bacterial cultures in such a way that 0.05 cc.—or one drop from a 1 cc. pipette—contains about 200 to 2,000 bacteria, and this inoculum is added to each tube. This size inoculum can usually be obtained by diluting an 18 to 24 hour culture to 10^{-4} to 10^{-8}, depending on the density of the growth. The tubes are incubated overnight, readings of gross clouding, hemolysis or other changes are made the next day, and subcultures taken on blood agar plates, to be read the following morning. The results of these subcultures are tabulated and the patient's course followed to see whether or not this test could serve as an indication of the clinical progress.

Some of the results of this preliminary study are shown in Table I.

RESULTS AND DISCUSSION

These tests were performed on a total of 35 patients with severe infections of various types, most of the cases having bacteremia. This series, of course, is too small and the observations too limited to warrant any conclusions about the possible value of the test. Moreover, it is impossible to set any definite level of bacterial inhibition as being an "adequate" level, as this obviously varies for each different infection. There is no reason to suppose, for instance, that a bactericidal level that is adequate for the control of an uncomplicated pneumococcal pneumonia with bacteremia is necessarily adequate in cases of subacute bacterial endocarditis, osteomyelitis or localized abscesses. Nor do we know how closely *in vitro* tests of this sort with drugs such as aureomycin, chloramphenicol, and the sulfonamides, which are mainly bacteriostatic, parallel results *in vivo*. Moreover there is experimental evidence to show that aureo-

mycin deteriorates rapidly at 37° C., losing 96% of its activity when incubated at this temperature for 18 hours (14). If we try to allow for these variables, however, and accept the criteria given by Schlichter (13), who considered a bactericidal level of 1:2 (i.e. complete inhibition in the first two tubes) as an optimal dosage, we can say that nearly all our patients whose progress was satisfactory did show adequate antibacterial levels or much higher. It was interesting to note that, though the titers were low in most of the patients receiving aureomycin alone, there was one test in which the organisms were killed at a titer of 1:4 and another at 1:16. This suggests that in these instances, at least, the serum-aureomycin mixture remained active, though incubated for the usual time of 18 to 20 hours. The same was true of 2 cases in which chloramphenicol was the only drug being used—in one of these the bactericidal titer was 1:4, in the other 1:16. We also found, in the 35 cases studied, that in 30 of them there was a good correlation between the patient's clinical condition and progress, and the results of the tests. These results are summarized and explained in Table II.

Similar experiments were set up with normal controls in which sera were obtained from 6 individuals having no apparent disease and 10 tests done with strains of bacteria which were being used in the other experiments. Ten of these were completely negative and 3 showed killing in the first tube. Eight patients with fever due to "influenza," pneumonia or malaria (none of whom were receiving antibiotics) served as "febrile controls." Ten experiments were carried out with this group—again using organisms currently under study—; 8 of these were negative and 2 positive, but only in the first tube.

The finding of a "prozone" was referred to in Table I and was noted in 4 cases. In these tests there was growth in subcultures from one or more of the first tubes, whereas the next 2 or 3 tubes would be sterile. This seemingly paradoxical finding is reminiscent of some experimental work of Kirby (7), and later reports by Eagle (8, 9). The former found that some strains of staphylococci were killed more rapidly by low than by high concentrations of penicillin. This may be due to the fact that the organisms are able to start active growth in the higher dilutions of penicillin and at that stage are more susceptible to its action. Eagle found the same to be true for several other types of bacteria and described an "optimal zone" for penicillin's bactericidal action, concentrations above or below this zone being relatively ineffective. Schlichter (13) mentioned the possibility of this effect as a result of unnecessarily high levels of penicillin, but did not find it in any of his cases.

This zone phenomenon may be of only academic interest, as even with large doses the blood levels of penicillin vary so much that in nearly all cases these levels are not apt to exceed the optimum range for long periods of time. It should be borne in mind, however, in these days when the tendency is to give massive doses of penicillin in hopes of overwhelming the infection rapidly,

TABLE I

Results of Studies on Sera of Six Patients with Acute Bacterial Infections

NAME NUMBER AND AGE	DATE	DIAGNOSIS	BACTERIUM ISOLATED	ANTIBIOTICS (DAILY DOSE)*					CONDITION OF PATIENT AT TIME OF EXPERIMENT	ANTIBACTERIAL ACTIVITY OF SERUM		INOCULUM (0.05 cc)	REMARKS AND RESULTS
				Pen.	Aur.	Strn.	Chl.	Sulf.†		Killed	Inhib.		
1. L. G. 526838 62	3/11/50	Rheumatic heart dis. S. B. E.	α-strep. fecalis	2.4	3				Good (cultures negative)	1:8	1:32	10^{-6} (610)‡	"Prozone" noted (see text) Resistant to penicillin (31 u.) Infection cured
2. V. F. 497217 24	11/10/50	Bacteremia Pyarthrosis Acromegaly Diabetes mellitus	Staphylococcus aureus				4		Fever still	1:4		10^{-6}	Resistant to penicillin
										1:1 → Joint fluid		10^{-6}	
	11/17/50						6		Better, but fluid in joint still	1:2			Bacteremia cleared quickly but joint infection responded slowly
										1:4 → Joint fluid		10^{-6}	
	11/29/50						10		Better, but fluid in joint still	1:4	1:8	10^{-6}	Finally cured
										1:4	1:8 → Joint fluid		
3. T (H. L. H.) 4	7/22/50	Bacteremia Meningitis	H. influenzae (Type B)		0.5			2.7	Poor	0	0	10^{-4}	Test indicated no antibacterial effect Died

4		Meningitis	(Type B)										Died

4. M. F. 574154 40	6/9/51	Meningitis Cellulitis of arm	H. influenzae (Type B)				4		Better, but fever still	1:16	1:32	10^{-2} (2 hr. cult.)	Adequate level on blood and spinal fluid
	6/16/51						6		Good. Temp. almost norm.	1:8 1:8	1:16 1:16 → Spinal fluid	1:2 (3,000)	Responded well Cured
5. D. R. A77898 5	5/25/50	Brain abscess Congenital heart disease	Anaerobic β-Strepto-coccus	1.6	1.1			2	Improved. Two large abscesses drained	1:32		10^{-4}	Hemiplegia nearly cleared at discharge. Infection cured
6. P. P. 454597 72	6/9/50	Bacteremia Cirrhosis of liver	α-Strepto-coccus (Micro-aerophilic)	1.2			3		Temp. dropped and much improved	1:64		10^{-2}	Equally good response with penicillin and combination. Infection cured
	6/19/50	Diverticulitis		1.2						1:32		10^{-2}	

* In millions of units for penicillin; in grams for others.
† Type not specified; usually gantrisin or sulfadiazine.
‡ Numbers in parentheses refer to number of organisms, when counted.

that we may actually at times be overtreating the patient, rather than just wasting penicillin. In one of the 4 cases (Case 5, Table I), the "prozone" was noted in a patient receiving 4 grams of aureomycin per day (no reference to this has been noted previously), but it indicates that other antibiotics besides penicillin may have an optimal zone for their antibacterial effect.

Such findings make it seem all the more important to adopt a test which will give us more direct information on the antibacterial potency of serum when one, or particularly when multiple antibiotics are being given. This is a method which may help us to determine whether the drugs are acting synergistically or antagonistically and thus serve as an additional guide in therapy of this sort. The test may also prove of value in measuring the antibacterial levels of body fluids of patients during therapy, as was done in the spinal fluid of one patient and the joint fluid of another. It may likewise help to determine whether or not the patient's fever could be due to a drug reaction rather than the infection in a case in which the temperature remains up in the presence of an adequate serum activity, as was noted in one patient.

TABLE II

Relation of Activity of Sera to Clinical Efficacy

	CLINICAL CONDITION OF 35 PATIENTS AT TIME OF TEST	
	Satisfactory	Poor
Sera active	26	4*
Sera inactive	1†	4

* Fever in one case probably due to penicillin reaction; good response to aureomycin. Continued fever in one case, presumably due to Hodgkins's disease and in another to leukemia. Fourth case moribund at time of test; had overwhelming infection and endocarditis due to staphylococcus—resistant to penicillin (3.1 u.).

† Patient receiving aureomycin for pneumococcal pneumonia; responded slowly, but got well.

It is obvious that such results as have been obtained in this study are not conclusive and must be considered preliminary in nature. It is hoped that the test may be tried in other clinics so that a sufficient number of observations can be collected to determine whether or not it is of value.

SUMMARY

1. Antibiotic and chemotherapeutic agents are being used in various combinations with increasing frequency in the therapy of acute bacterial infections of all types.

2. A review of recent reports indicates that some of these agents act synergistically against bacteria but that others may be antagonistic, depending to a large extent on the proportions and dosages employed.

3. In severe and complicated infections it is not always possible to predict

which of these effects we should expect, and the usual *in vitro* tests may not be adequate therapeutic guides.

4. A more direct method is described in which the antibacterial activity of the patient's serum is titrated against the infecting organisms.

5. The correlation between this test and the clinical condition of the patient at the time of the test was good in 30 of 35 cases studied.

6. A seemingly paradoxical "prozone" phenomenon was noted in 4 tests; the possible significance of this is discussed.

7. Such a test would seem to be indicated as a guide to therapy of severe bacterial infections of all types, particularly those in which multiple antibiotics are being employed, and when the clinical response is unsatisfactory.

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MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

HURD HALL, JANUARY 14, 1952

Dr. Grafflin: The meeting will please come to order. The first paper is by Drs. Lytt Gardner, Clyde Migeon, Samuel H. Silverman and Lawson Wilkins. The paper will be presented by Dr. Gardner.

DIFFERENTIAL DIAGNOSIS OF ADRENOCORTICAL TUMOR AND ADRENOCORTICAL HYPERPLASIA

The colorimetric technique devised by Allen, Hayward and Pinto for dehydroisoandrosterone-like compounds in urine (DHIA steroids) has been used to help differentiate between congenital adrenal hyperplasia and virilizing adrenal tumor. Congenital adrenal hyperplasia in the female usually offers no difficulty in diagnosis since the patients exhibit a urogenital sinus. Congenital adrenal hyperplasia in the male must be differentiated from other causes of male precocity, of which virilizing adrenal tumor represents a most important differential diagnosis. The authors have determined on cases of congenital adrenal hyperplasia and virilizing adrenal tumor: (a) Urinary excretion of 17-ketosteroids, which was abnormally high in all cases; (b) Urinary excretion of DHIA steroids, which was normal in most cases of hyperplasia, slightly elevated in two cases of hyperplasia with hypertension and much elevated in cases of tumor; and (c) Spectrophotometric curves (300 mμ to 700 mμ) of the DHIA reaction, which showed great differences between cases of hyperplasia and cases of tumor. When cortisone treatment was instituted in these various conditions: (a) The urinary excretion of 17-ketosteroids was brought down to normal in the cases of hyperplasia, but did not fall in the cases with tumor; (b) The urinary excretion of DHIA steroids in the cases of tumor was not decreased by cortisone. In the two cases of hyperplasia with hypertension which excreted a small excess of DHIA steroids, this group of steroids completely disappeared from the urine on cortisone treatment and blood pressure became normal. No patients with Cushing's syndrome were in the foregoing groups. One case of Cushing's syndrome with malignant adrenal tumor excreted excess 17-ketosteroids but no excess of DHIA steroids. The 17-ketosteroid output of this case was not diminished by cortisone therapy. It would appear that three new procedures are available to help differentiate between congenital adrenal hyperplasia and virilizing adrenal tumor: (1) Response of 17-ketosteroid excretion to cortisone; (2) Response of DHIA steroid excretion to cortisone; (3) Spectrophotometric curves of the DHIA reaction.

Dr. Grafflin: Dr. Wilkins, would you care to say anything about this?

Dr. Wilkins: There is little I have to add to what Dr. Gardner has said except to point out again the value of his observations from the standpoint of clinical differential diagnosis. In the past a great proportion of the cases of hyperadrenocorticism have had to be explored because of the possibility of tumor. In females with adrenogenital syndrome when the condition arises in fetal life and there are abnormalities of sex differentiation with a persistent urogenital sinus and hypertrophied clitoris, one can be sure that there is hyperplasia and not tumor. On the other hand females who have normal sex differentiation at birth and become virilized later with hypertrophy of the clitoris and hirsutism might have either adrenal tumor or hyperplasia. Likewise, in males one cannot differentiate clinically the type due to diffuse hyperplasia from the type of virilization that develops in early childhood due to an adrenal tumor. The methods described permit this differentiation without exploratory operation. We feel quite sure that when one gets a definite response to cortisone with sup-

pression of the 17-ketosteroids the condition is due to hyperplasia rather than tumor. This work has been confirmed elsewhere. In Cushing's syndrome we are still at a complete loss in regard to the differentiation of the two without exploration because, as Dr. Gardner has pointed out, there is no special increase in dehydroisoandrosterone and no suppression of 17-ketosteroids by cortisone in the cases of Cushing's syndrome due either to hyperplasia or to tumor. It is still necessary in Cushing's syndrome to explore for the possibility of tumor.

Dr. Grafflin: Dr. Howard.

Dr. Howard: I can only ask a question of Dr. Gardner and perhaps it is inapropos. He mentioned a number of our patients with hirsutism without virilism. I wonder if he would care to comment on whether those patients have this material in their urine or not and if so what has happened when cortisone has been given to those individuals.

Dr. Gardner: We have had the opportunity of examining the urine steroids from a number of adult females showing hirsutism without virilization who are being studied clinically by Dr. Howard and also by Dr. Seegar-Jones. These patients have total urinary 17-ketosteroids either in the normal range or slightly elevated. Some of these cases show spectrophotometric curves of the DHIA reaction which are quite comparable to normal individuals. However a few of these cases show spectrophotometric curves with either a small peak at 600 mμ or a plateau between 470 mμ and 600 mμ. Cortisone therapy completely obliterates this peak or plateau and in every such case I can recall has brought the 17-ketosteroid excretion down to values under 10 mg. per day. Only a few cases have been studied in this way, but I think this represents a very significant finding.

Dr. Grafflin: Is there any further discussion on this paper? If not we will go on to the second paper. This was supposed to have been given by Dr. R. K. Burns, Jr., but he is rather ill with a respiratory condition this evening and can't talk and Dr. William L. Straus, Jr., of the Department of Anatomy has kindly consented to speak in his place. I want to say for Dr. Straus before he speaks he has had about 6 hours' warning and I am delighted that he has decided to come. He will speak on

RECENT DISCOVERIES BEARING UPON THE EVOLUTION AND ORIGIN OF MAN

Recent fossil discoveries in Asia and South Africa are discussed.

The Asiatic forms are *Pithecanthropus*, an early type of actual man, and an apparently contemporaneous huge manidbular fragment, termed *Meganthropus*—both from Java—and giant teeth from China, termed *Gigantopithecus*. The African forms are the Australopithecinae, comprising remains of three supposedly distinct but related genera—*Australopithecus*, *Paranthropus*, and *Plesianthropus*.

The Asiatic specimens, *Gigantopithecus* and *Meganthropus*, have been regarded by Weidenreich as indicating that the ancestors of the modern type of man were giants. The recent discovery of a number of massive Australopithecine skulls (termed *Paranthropus crassidens*) in South Africa adds interest to this problem. The possible significance of these giant forms is considered.

The Australopithecinae, exhibiting an interesting mixture of hominid, anthropoid, and monkey characters, have been regarded by Broom and others as fully erect bipeds closely akin to man. But this enthusiastic conclusion is open to question, and alternative interpretations cannot be ignored.

As a result of recent fossil discoveries, the evolution of man appears to have been more complex than it seemed a quarter of a century ago.

Dr. Grafflin: Dr. Corner, would you care to comment on this paper?

Dr. Corner: Dr. Grafflin, Ladies and Gentlemen: I suppose Dr. Grafflin called on me to comment on this paper because I am an anatomist, but an anatomist of the kind whose life has been spent in looking at tissues and organs through the microscope is not necessarily qualified to discuss such topics as fossil man and ancient giants. I can only say that having been an interested observer of studies of human evolution during the past generation and more, I have been, like everyone else, puzzled by much of the recent literature and therefore am grateful to Dr. Straus for his clear and instructive review. He deserves our special thanks for speaking on very short notice. My colleague, Dr. Burns, who was so unfortunate as to come down with acute laryngitis this morning, would I am sure wish me to express to the audience his disappointment at not being able to speak and to thank Dr. Straus for filling his place so effectively.

Dr. Grafflin: Is there any other discussion of this paper? After this performance I would like to tell Dr. Straus that I regard 6 hours as more than enough warning. The final paper is by Drs. George Dana, Stanton Eversole and Charles Zubrod and will be presented by Dr. Dana.

THE CLINICAL ENTITY OF RETINAL ANEURYSMS, GLOMERULAR NODULES AND HYPERGLYCEMIA

A comparative study was presented of the metabolic features of diabetes mellitus in patients with and without glomerular nodules of the Kimmelstiel-Wilson type. The charts of all adult patients with diabetes mellitus autopsied at the Johns Hopkins Hospital in the years 1938–50 were reviewed and their kidney sections studied independently. These 190 diabetic patients were divided into two groups according to the presence or absence of glomerular nodules. The results of the study have been built around three components, namely diabetic acidosis, glomerular nodules, and diabetic retinitis of the capillary aneurysmal type.

In the 57 patients with glomerular nodules there was a rarity of diabetic acidosis in contrast to its common occurrence in the 133 controls. Both groups experienced recurrent stress such as infection, gangrene and insulin withdrawal. 90% of the patients with glomerular nodules showed the presence of retinal aneurysms in contrast to 10% of the controls. It is probable that retinal aneurysms are an intrinsic part of the same entity as glomerular nodules and it is likely that the primary disturbance consists of aneurysmal dilatations of the capillaries. In this series there was no single instance of an acidotic episode in the patients with both retinal aneurysms and glomerular nodules. Since these patients did not develop ketosis in the absence of exogenous insulin, it was concluded that they have an adequate supply of endogenous insulin. It was thought that patients with retinal aneurysms and hyperglycemia would not develop diabetic acidosis when their daily insulin was withheld. In a preliminary clinical study, five typical patients were selected and each studied for 3–5 weeks with no lowering of the CO_2 combining power.

Relative excess of the hyperglycemic-glycogenolytic factor in a patient with near normal endogenous insulin can explain adequately the metabolic defect of hyperglycemia without acidosis, and may also be the causal factor for the capillary damage either directly or indirectly. Studies are now in progress to determine the role of disturbances in the alpha-beta cell ratios in the production of diabetic capillary aneurysms.

This report constitutes a suggestion of a specific association of capillary aneurysms of the retina, hyperglycemia without acidosis, and nodules of the glomeruli. These patients constitute at least one-fourth of the diabetic population.

Dr. Grafflin: Dr. Zubrod, would you care to comment on this please?

Dr. Zubrod: Dr. Grafflin, I would like to make clear the two points we tried to establish in giving this report. The thinking about clinical diabetes has always centered around

insulin deficiency, and thus patients with severe diabetes are supposed to have complete destruction of the islets with relatively complete deficiency of insulin and patients with mild diabetes are supposed to have partial or incomplete destruction of the islets with mild deficiency of insulin. Granting the argument of Dr. Dana that mild diabetics must have some endogenous insulin, we are presented with this paradox, that the patients with complete insulin lack rarely if ever develop the combination of retinal anuerysms and glomerular nodules, whereas those patients with a mild deficiency of insulin commonly and severely develop these complications. Our first point is that the presence of the combination of diabetic retinitis and glomerular nodules can not be explained by simple insulin deficiency. Secondly, the experiment of von Mering and Minkowski in removing the pancreas and producing diabetes has in terms of modern knowledge turned out to be a very complex experiment. This is because complete pancreatectomy removes two hormones, insulin and hyperglycemic factor, which probably act together to maintain the normal blood sugar concentration. Our second point is that in mild diabetes granting that these patients have incomplete destruction of the islets, the interplay of the hyperglycemic factor and insulin must be taken into consideration in explaining the metabolic defect and in explaining the capillary disease.

Dr. Grafflin: Dr. Eversole.

Dr. Eversole: Dr. Grafflin, I would like only to say that I have been keenly interested in staining differentially the alpha and beta cells in this pathological material. Because of the fixatives we use and also autolytic changes in the pancreases this has not been accomplished to our satisfaction. Possibly it can be done only in biopsy material. We are also working on it from an experimental point of view in animals. This approach at an early stage in the experiments looks promising. Of course differential islet stains here will be no problem.

Dr. Grafflin: Dr. Harvey.

Dr. Harvey: I think all of us who know about these observations of Dr. Dana and Dr. Zubrod and Dr. Eversole and the hypothesis which they put forth have found them extremely stimulating. Obviously there is much more work to be done before the final chapter can be written, but there are other observations which to me give a great deal of added emphasis to what they have concluded thus far. One is the situation in regard to the effect of ACTH. It is known that ACTH or cortisone produces hyperglycemia. Those patients, however, do not tend to develop acidosis. Also as Dr. Rich has demonstrated in the experimental animal given cortisone, renal lesions develop which are similar to the Kimmelstiel-Wilson nodules in these patients described tonight. Also, less well documented because no pathological observations are available, one or two patients under treatment with ACTH have been seen to develop retinal lesions which clinically resemble the capillary lesions that are seen in patients with diabetic retinitis. Also one patient treated with ACTH who subsequently died had the typical Kimmelstiel-Wilson lesions in the kidney. There are many comments and questions that could be made. I am going to leave other specific questions to the endocrinologists.

There is one thing about this work just as thrilling to me as the observations themselves and the hypothesis that has been put forward. Particularly since the war there seems to have grown up a very strong conviction on the part of a great many people that the only way to accomplish advancements in science at a rapid rate is to raise a great deal of money for research and it has become almost a fashion even among the younger individual starting out in a research career to feel he has to have a large grant of money, expensive apparatus, technical help, etc. I think as you go back over the history of important scientific advancements most of these came through simple observation. To me the most thrilling part of this whole piece of work is the originality shown in the observation of patients, careful study of clinical records; leading to what may turn out to be one of the most important advances of recent years if this work can be fully substantiated. It was accomplished up to this point

without any research grant and without any apparatus except the human brain. Thus, in addition to the important work and the great advances made in the laboratory, there is still much to be accomplished by intelligent clinical study of disease processes.

Dr. Grafflin: Dr. Howard.

Dr. Howard: I don't know where to begin, Dr. Grafflin, in discussing this paper. Carried to its ultimate conclusion, Dr. Dana's suggestion would mean that pancreatic alpha cells cause diabetic aneurysms both in eyes and kidneys and that pancreatectomy might stop this process. However, one would then substitute a susceptibility to acidosis and almost certain diarrhea for the vascular lesions.

Clinicians interested in diabetes have for a long time felt helpless in the face of the degenerative lesions which seem to come so frequently with time in this disease. In some patients with diabetes of 30–40 years' standing, however, no such lesions appear. Any clue to causative mechanisms involved in their production is a great step forward.

Diabetes is a syndrome, not a disease, and some clinicians now define the diabetic state as one with a tendency to hyperglycemia and ketonemic acidosis. Patients with seemingly the same "degree" of diabetes as judged by insulin requirement may differ widely in other ways. The classic study of Atchley, Loeb and their confreres at Presbyterian Hospital demonstrated this point well. Two volunteer students were well regulated on the metabolism ward with almost identical diets and insulin dosage. Insulin was then withdrawn. In one patient after four days severe acidosis supervened and insulin had to be resumed; the other patient was hardly sick 11 days after insulin was stopped. Perhaps this second patient had what Dr. Dana is talking about, and it would be interesting to find out if this man now has diabetic retinopathy, the other not.

It is of some interest, as Dr. Harvey has mentioned, that diabetic patients who receive cortisone or ACTH fail to develop ketonemic acidosis, though their hyperglycemia and glycosuria are greatly increased. This has been assumed to be due to better utilization of ketone acids by persons under cortisone. Patients with Cushing's syndrome, usually relatively insulin resistant, also seldom go into diabetic acidosis.

The function of alpha cells has been speculated on for some time. American insulin contains a hyperglycemic factor supposed to be derived from them; a Danish insulin called Novo is the only one that does not, so far as I am aware. Insulin derived from fetal pancreas, in which alpha cells haven't developed, doesn't contain the hyperglycemic factor; nor do extracts of duct-ligated pancreas. Alloxanized pancreas, however, contains the hyperglycemic factor in relatively large amount. So alpha cells are thought to produce it. Whether or not sustained hyperglycemia produced by this substance is accompanied by ketonemic acidosis or not, I do not know; if one of the authors knows it would be interesting to learn, and if no acidosis develops it would strengthen their hypotheses, I think.

Dr. Grafflin: Dr. Friedenwald.

Dr. Friedenwald: I have been very much stimulated by this presentation and have had the privilege of following conversational reports from Dr. Dana and his co-workers from time to time. It seems to me that they have firmly established two things about the disease in which the ophthalmologists are interested in relation to diabetes. In the first place it is entirely clear now that the retinal lesions and the kidney lesions are one and the same disease. The correlation which they have been able to show in their cases are even closer than Dr. Day and I were able to show two years ago. At that time we compared pathological diagnoses of diabetic retinopathy with the findings on routine sections of kidneys from the autopsy files. Drs. Dana and Eversole have compared the clinical diagnosis of diabetic retinopathy with very careful and extensive histologic studies of the kidneys. It is no wonder that we found a higher incidence of retinopathy and a lower incidence of nephropathy than they did.

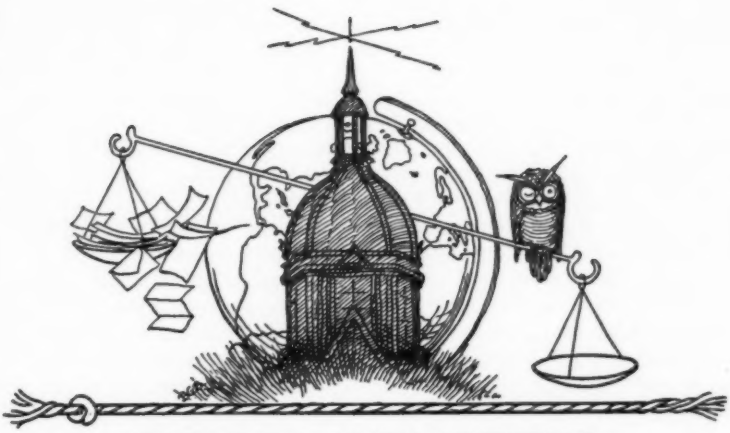
In the second place Dr. Dana and his co-workers have shown that among adult diabetics,

the diabetes runs a different course in those individuals who develop the characteristic diabetic retinopathy and nephropathy from that in patients unaffected by these specific vascular lesions. It has long been thought that something extra happens to the diabetic as a result of his long diabetes which might account for the retinal lesions, but occasional cases appear in the ophthalmology clinic which contravene this hypothesis and support Dr. Dana's conclusion that their diabetes is fundamentally different. Dr. Becker on the staff of the Wilmer Institute recently encountered a patient who presented the characteristic ophthalmoscopic features of diabetic retinopathy and in whom there was no demonstrable evidence of diabetes. The patient had no glycosuria, normal blood sugar and normal sugar tolerance curve. This patient was sent home with the diagnosis undetermined, and came back in 6 months with a severe diabetes. Surely it was not the duration of the diabetes that caused the retinal lesion in this case. Dr. Dana, Dr. Zubrod, and Dr. Eversole I think have raised the first reasonable clue of the possible metabolic difference between diabetics with and without retinopathy.

Dr. Grafflin: Dr. Rich.

Dr. Rich: Dr. Grafflin, I think it superflous to say that this is an extremely interesting series of observations, and I am sure that we all hope that further work will support the hypothesis that has been put forth. There are many suggestive things about which the authors have not talked tonight which given one reason to hope that it will so turn out. The status of the relation of the alpha cells to the observed phenomena must, of course, await the results of the pathological-histological and pathological-physiological studies which are now in progress. It is unfortunate, as Dr. Eversole has said, that it is not easy to study the alpha cells and the beta cells of the islets of Langerhans in autopsy material. It would be an immense help if that could be done. Dr. Eversole has worked extremely hard in the effort to stain these different types of cells in the autopsy material of these cases, and I can say that we have been able to obtain the best conceivable control that the failure to obtain satisfactory stains on this material is not due to any fault in Dr. Eversole's technique, since Dr. Gomori, himself, very generously tried to stain some of this material, but without success.

Dr. Grafflin: If there is no further discussion I declare the meeting adjourned.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

The Collected Papers of Adolf Meyer. Four Volume Set $30.00. Edited by EUNICE WINTERS. Vol. 3, Medical Teaching. With an introduction by FRANKLIN G. EBAUGH. 577 pp. *The Johns Hopkins Press, Baltimore Md.*

The third volume of this series presents Dr. Meyer's papers on medical education, and includes an additional section containing fifteen biographical sketches or obituaries of important medical personages written by Dr. Meyer. This curious combination in one volume may serve to sharpen the reader's appreciation of a significant point.

In his difficult struggles with the problem of teaching, Dr. Meyer viewed the medical student in his prospective role of physician, charged with responsibility for action in the care of patients, and needing conscientious preparation for this role. Had he been easily satisfied, Dr. Meyer could have simplified his teaching task by orienting it more simply to the presentation of available psychiatric subject matter, of which he had an extraordinarily penetrating knowledge. He chose instead the larger and harder task of guiding the medical apprentice's hands and vision toward the major responsibilities for patients as persons. For this task he needed a subject matter not yet appropriately developed and organized, and many of the teaching difficulties in such an endeavor are clearly manifested in the materials in this volume. The work brought together here reveals Dr. Meyer trying to prepare medical students as they come—good, bad and indifferent—for the deep understanding, responsible care, and wisely melioristic guidance of patients as persons, at that ideal level of excellence which is only partially and imperfectly foreshadowed in the mature professional careers of those outstanding persons whose lives are outlined here in his biographical sketches! A difficult ideal, inevitably involving some frustration!

Meyer's major creative endeavor, in the service of this purpose, was the development of the teaching of what he called psychobiology,—most cogently presented to the medical profession at large in 1915 in the *Journal of the American Medical Association*, in a paper

entitled "Objective Psychology or Psychobiology with Subordination of the Medically Useless Contrast of Mental and Physical,"—the fourth article in this volume, pages 38–43. The essence of this article is in the sentence: "As soon as mental attitudes and mental activities are accepted as definite functions of a living organism, mentation and behavior is treated as a real chapter of the natural history of man and animal, and psychology ceases to be a puzzle supposedly resisting the objective methods of science." Objections can be made to this sentence. Psychology did not in fact cease to be rather puzzling, despite this flash of insight. Grammatical purists might also object to the singular verb "is" for the two subjects "mentation and behavior," but this apparent grammatical slip reveals the essence of his proposition, namely, that "mentation and behavior" is actually one subject.

From an earlier address in the same decade is taken this quotation:

"Some of us feel that in the life of the individual and in interindividual relations reactions occur and determine developments to which neither anatomy nor physiology in their narrow sense can do justice, but in which we are forced to speak in terms of a psychology or at least a biology which is able to scrutinize the reactions of behavior and mentation, the conditions under which they occur, and their effects in the course of the life and behavior of the organism that shows them. We study deliriums, depressions, dominant ideas, delusions and obsessions for the role they play, the conditions under which they arise, the effects on the stream of mentation and mental balance, and their modifiability," (p. 25). Also, p. 35, "The chief weight (in the clinical training of the medical student) is to be laid on the known conditions of modifiability of the integrative factors of adaptive reactions."

Thus, in speaking with his colleagues about what he was trying to do in his teaching, Meyer could speak with crystal clarity; his expression and organization of thought become, however, heavily involved, and somewhat obscured by neologisms, in "The Teaching Materials," much of which is reproduced in this volume. Large sections of these "Materials" are of historical interest, such as the portions on "ergasiology" and "ergasiatry," and the first-year outline for self personality study. These detailed instructions serve well to indicate the sort of working obligation implied by Meyer's preference for reaction type formulations rather than disease entity diagnoses, and thereby make it abundantly clear that he was not simply inventing new words for old ideas.

Of much interest in this connection is a remark of Meyer's in his 1933 Maudsley Lecture, included in the present volume. He said (p. 404): "At that time (the early 'nineties) it (psychiatry) appeared, and in fact it still appears, to be a field somewhat disturbing, because it seems to demand unusual talents of verbal formulation; and it is apt to be forbidding because even today it is almost unintelligibly obsessed by epistemological dogmatism. I remember that even in 1892 I definitely rejected the advice to take up psychiatry in Switzerland because I felt it required much more ability than I had for verbal expression, rather than opportunity for concrete demonstration through action."

The key position in the present volume, pp. 1–20, has been assigned, with much editorial wisdom, in the reviewer's opinion, to "The 'Complaint' as the Center of Genetic-Dynamic and Nosological Teaching in Psychiatry," summarized thus: "With my students and coworkers I cultivate much more conscientiously than ever 'the complaint' as offered by the patient and the lay observers and family and the family physician that are 'put to it,' and confronted with more or less real situations and most apt to be critical and inquiring; and I include in 'the complaint' the facts one determines with one's own growing experience in the taking of the history of the present illness, its setting and antecedents, the early history and the family history and the personality makeup and assets. This keeps the problems of the case close to the facts which I allow to stare me stubbornly and provokingly in the face; it tends to keep before us the therapeutic problem of the patient and nurses

and physician in charge, the short-term and long-term problems of management, and the assets as well as the actual difficulties, the course, and the probabilities of outcome, and the formulation for the family and the patient, and the best technical statement."

In the perspective afforded by these collected papers, the high degree of complexity and a certain awkwardness of phraseology in Meyer's statements can be viewed as the unfortunate consequence of a somewhat excessive zeal for completeness and thoroughness. Meyer's outstanding contribution to medical education, as exemplified in this volume, lies in the nobility and breadth of his conception of the physician's responsible duty and the scientific opportunity to study and help distressed and disabled persons.

JOHN C. WHITEHORN.

Differential-Diagnostische Symptomatologie. By W. CATEL. 640 pp., Ganzleinen DM 69. *Georg Thieme Verlag, Stuttgart, Germany.*

This book differs from most textbooks for pediatrics in that the various diseases are discussed under the headings of major symptoms, rather than by organ systems. It is a clear-cut presentation with excellent illustrations, diagrams and tables. There are a few areas which reflect the lag in German postwar medicine. For instance, there is no mention of unipolar electrocardiography, and electroencephalography is omitted completely. This book would be a helpful addition to the library of any German student or practitioner but there is nothing in its content which is not available in English for those who do not read German easily.

F. F. S.

Medical Milestones. By HENRY J. L. MARRIOTT. Foreword by SIR ALEXANDER FLEMING. 293 pp., $3.50. *The Williams and Wilkins Co., Baltimore, Md.*

In his foreword Dr. Fleming credits Dr. Marriott with a task well done, the task having been to tell the truth about some of the new chemotherapeutic agents without benefit of sugar-coating or soap opera. This reviewer would agree completely and would add that such an undertaking has been long overdue. No one would deny that the discovery of the antibiotics, the new treatments for anemia, the developments in heart surgery, the chemical warfare on cancer, the modern drug therapy of leprosy, the use and potentialities of ACTH and cortisone, the production of DDT, and the discovery of dramamine have brought about phenomenal advances in medicine. But overenthusiastic, unscientific, or premature reporting of "miracle" drugs can be only detrimental to medical progress and deceptive to the lay public. The case in point which Dr. Marriott has the courage to bring out is the unsavory story behind the antihistamine "cold cure" bubble.

As for style, the author has a talent which is not too common, that of combining scientific accuracy with readability; and when he has to use a term which might be unfamiliar to the lay reader, he writes a footnote then and there instead of hiding it away in a glossary at the end of the book. *Medical Milestones* is no scientific or literary milestone but it is timely, readable, and serves the purpose of its author very well.

C. A. C.

Handbook of Nutrition, 2nd Edition. A symposium, prepared under the auspices of the Council on Foods and Nutrition of the American Medical Association, 1951. 717 pp., $4.50. *The Blakiston Co., Philadelphia, Pa.*

The present edition of this valuable handbook is divided into four parts. Part I deals with individual nutrients such as protein, fat, carbohydrate, minerals, and vitamins. Part II deals with nutritional needs which include recommended dietary allowances, energy requirements of adults, feeding of healthy infants and children, and nutritional problems

during pregnancy and lactation, in geriatric medicine and in illness and disease. In Part III, the various nutritional deficiencies such as those minerals, water-soluble and fat-soluble vitamins are included. Three chapters are devoted for the discussion of deficiencies in terms of imbalance and dietary relationships in nutrition, caloric undernutrition and starvation and fluid therapy. Part IV is devoted to the discussion of foods and their nutritional qualities, including chapters on adequacy of American diets, foods of plant and animal origins, food for emergencies and improving the quality of cheap staple foods. Since the science of nutrition has moved at an accelerated pace during the past few years, the publications are often dispersed and not available to those who could profit by reading them. This book, in which experts prepared review articles, should be valuable to all students of nutrition. However, it must be pointed out that because of the coverage of a wide, if not entire area on nutrition, in a limited number of pages, the chapters on specific topics are by necessity extremely brief and in some cases, the newer concepts are not included. For example, in the chapter on "Proteins in Nutrition," an adequate discussion on the time factor or the recent reports on accessory factors in relation to protein synthesis might be included, if more space were available. Similarly, in the chapter on trace elements, the discussion on the element cobalt for animal nutrition could be expanded and brought up-to-date by bringing in the importance of synthesis of vitamin B_{12} from dietary cobalt by the micro-organisms in the flora.

B. F. C.

Handbook of Diseases of the Blood. By A. PINEY. 213 pp., $5.00. *J. B. Lippincott Co., Philadelphia, Pa.*

The author of this little book has attempted to produce a simplified version of hematology, clinically oriented for the use of the practicing physician. The initial chapter deals with the routine physical examination, pointing out the various abnormalities encountered in patients with blood dyscrasias. A second remarkably brief chapter reviews the laboratory methods employed in the study of such patients. The remainder of the book consists of a conventional series of short and inadequate descriptions of blood diseases. Numerous inaccuracies and misleading statements are found. One is surprised to find that the normal range of the hemoglobin concentration of the blood is stated to be 90 to 96%. Probably because of a printer's error, the megaloblastic anemias are included under the heading of "Iron Deficiency" in the chapter on types of anemia. The hypochromic anemia associated with hiatus hernia is attributed to defective absorption of iron, and the fact that bleeding from these lesions is common is not mentioned.

Because of the inadequacies and inaccuracies, it seems unlikely that the alert practitioner will be satisfied with the information which this volume provides.

C. L. C.

Conteben Bei Lungentuberkulose. By H. KLEESATTEL AND W. GÜRICH. 154 pp., Kartoniert DM 22.50. *Georg Thieme Verlag, Stuttgart, Germany.*

Following the suggested beneficial effect of the thiosemicarbazones in the treatment of tuberculosis by Domagk in 1946, these compounds have had extensive clinical trial, particularly in Germany. This monograph summarizes the clinical investigation by the authors over a three year period with Conteben (TB1/698, 4-acetylaminobenzaldehyde thiosemicarbazone), known here as Tibione, Myvizone, or Amithiozone.

The agent was used conjointly with other non-chemotherapeutic control measures in the treatment of 160 selected cases of which 40 were reviewed in limited detail. The majority fell into our "far advanced disease" category. The authors felt the drug had a dominating, beneficial influence on the disease in about 18% of their cases, but was curative in none. The most significant responses occurred in fresh exudative disease, whether intra- or extra-

pulmonary. Little benefit was observed in productive or caseous disease. Postoperative spread was not prevented, and on occasion lesions flared up under the aegis of the drug.

Duration of treatment was conditioned by clinical progress. Emphasis was placed on the necessity for individualization of dosage, and for hospitalization of the patient during treatment. Oral administration was used except for local instillation into empyema cavities, where it was found to be effective.

Toxic effects were noted in over 50% of the cases studied, necessitating discontinuation of the drug in 10–15%. Hepatic injury accompanied by jaundice, gastrointestinal disturbances, diabetes mellitus, marked and divers haemotoxic and haemorrhagic manifestations, and renal alterations were observed. Toxicity appeared to be dependent on both the daily and total amount of drug administered.

The rather remarkable result obtained that all cases of diabetes produced or exacerbated during the administration of the thiosemicarbazone showed reversal of the observed abnormalities of the blood and urine during the administration of desoxycorticosterone. (Rössler has demonstrated damage to the adrenal cortex in animals fed with TB1/698). Unfortunately, no endocrine tissue was taken at obduction for histological study in the five cases expiring from all causes during the period of observation. The reviewer was particularly interested in the implications of these phenomena regarding the pathogenesis of the diabetes, the mechanism of action of the drug, and the potential use of the agent as an experimental diagnostic tool.

While this thiosemicarbazone has the same general pathological areas of use as does streptomycin, its capriciousness in effect and marked toxicity make its use as an adjuvant in the therapy of tuberculosis subject to considerable circumspection. Other derivatives of less toxicity and/or increased efficacy may be forthcoming. The authors essayed no concomitant administration of Conteben and streptomycin, a combination found to be synergistic by Spain in this country. No increase in drug resistance by the organisms was observed, though it is known that 20% of organisms are insensitive to the drug in the doses clinically used. The study might have been made more effective had it been more comprehensively extensive and searchingly intensive.

P. W.

Penicillin Decade, 1941–1951, Sensitizations and Toxicities. By LAWRENCE WELD SMITH AND ANN DOLAN WALKER, 122 pp., $2.50. *The Arundel Press, Inc., Washington, D. C.*

Although penicillin is one of the least toxic drugs ever utilized in clinical medicine, "sensitivity reactions" (largely dermatological) and other undesirable side effects occasionally present real problems to the practitioner. A critical review of the reported reactions to penicillin, with orderly presentation of the scattered data on incidence, predisposing factors, mechanisms, and relation to types of preparations, dosage, route, etc., would be a useful addition to the literature. This short monograph cannot be said to fill the need.

It is a hodge-podge of summaries of published papers, thrown together with no semblance or order or critique. For example, a section entitled "Oral Reactions" will also contain data on blood levels achieved by oral administration. Another on "Megaloblastic Macrocytic Anemia" contains a paragraph on the use and abuse of antibiotics in perirectal suppurations! It is somewhat startling to find a section labeled, cryptically, "Driesbach"—apparently in honor of a negative report by an author of that name. Portions of the book (despite its title and stated aim) are devoted to penicillin in the treatment of infectious mononucleosis or megaloblastic anemia, recommended dosage schedules, and (at some length) to blood concentration studies on a new penicillin salt marketed by the drug house employing the senior author.

The desirable features of the book are its light weight and convenient size.

L. L.

Renal Function. Transactions of the Second Conference, Oct. 19–20, 1950. Edited by STANLEY E. BRADLEY. 178 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

This is the record of the second conference on renal function. In spite of the delay of nearly a year in publication, it contains a great deal of extremely timely information in seven papers and a stimulating discussion following each. The conference was devoted to the influences of the adrenal cortex and the pituitary on renal function. Specifically the subjects discussed were "Adrenal Cortical Hormone and Related Hormones in Water Metabolism," "Antidiuretic Factors," "Some Pituitary and Adrenal Influences on Renal Function," "The Actions of ACTH and Cortisone on Renal Function in Man," "The Excretion of Sodium in Relation to Glomerular Filtration," "Endocrine Factors in the Utilization of Glutathione" and "Bioassay of Sodium-Retaining Corticoids and Some Changes in Excretion of these Substances in Disease."

This conference, though on a more clinical level than the first one, nevertheless reflects the specialized interests of the contributors in various phases of renal function. The editing is not so carefully done as in the preceding volume. For example "200 mg. male rats" in the legend of Figure 22 and an instance (p. 154) where Dr. Schorr apparently answers his own question. The lack of clarity of the legends of Figures 22, 23, 24, 26 and 27 makes interpretation of them difficult. On the whole, however, the book is well done and is certainly worthy of thoughtful perusal.

E. H. D.

Problems of Aging. Transactions of the Thirteenth Conference, February 5–6, 1951. Edited by NATHAN W. SHOCK. 194 pp., $4.00. *Josiah Macy, Jr. Foundation, New York.*

Dr. Frank Fremont-Smith, medical director of the Josiah Macy, Jr. Foundation, refers to the Macy conferences, which by now must be familiar to everyone, as an experiment in communication. It cannot be doubted that this conference was a noble experiment from the viewpoint of the conferees. Prepared papers considered endocrine and cardiovascular aspects of aging, aging of the integumentary system, and problems relating to cell division. An additional ten per cent of the volume records certain administrative and organizational problems of concern to those engaged in the advance of gerontology.

As is usual in these reports, this is a verbatim reproduction of the conference. For those who conferred such stenographic notes must be valuable in recalling a clue to be pursued or a witticism to be enjoyed. For those who were not there, there is a certain reproduction of the flavor of the conference and even a kind of excitement as a new idea, born of intermingling of disciplines, evolves. Thus, it is suggested that at least three experiments will be conducted as a result of this conference.

On the other hand, if this volume were intended as a reference work for non-conferees it could have said what it had to with a great deal more economy and it might have been indexed. In these days of high prices, it would have been considerate to have presented the material on cheaper paper without a stiff binder and at low cost.

K. L. Z.

Kymographische Röntgendiagnostik zur Beurteilung des Herzens in Beispielen. By PLEIKART STUMPF. 120 pp., Kartoniert DM 25.50. *Georg Thieme Verlag, Stuttgart, Germany.*

The development of electrokymography has increased our appreciation of roentgenkymography and of the work of Professor Pleikart Stumpf of Munich who devised the multiple slit roentgenkymograph about 25 years ago. The 1936 text on roentgenkymography by Stumpf and collaborators is a valuable reference source. (Stumpf, P., Weber, H. H. and Weltz, G. A.: Röntgenkymographische Bewegungslehre innerer Organe. Georg Thieme

Verlag, Leipzig, 1936. Pp. 516). It is of great interest that the tracings derived from roentgenkymograms by a method called kymodensography (p. 24) are essentially electrokymograms; electrokymography merely permits such recordings to be derived at one step. Many of the patterns of heart movement "discovered" by electrokymography are described in this earlier source.

Stumpf's most recent publication on this subject is a 120 page monograph summarizing his experience since 1936 with roentgenkymography as applied to the study of the heart and great vessels. Stumpf's technique differs from that employed in this country in one basic and several minor respects. It is the grid which moves in his kymograph rather than the film; this is disturbing to the purist since by such a method one is recording movement not of one "point" (the term is used loosely) on the cardiovascular silhouette but rather of a constantly changing "point." (Stumpf correctly points out that even in the moving film method one "point" is not recorded from since rotatory and head-foot movement are continually changing the part of the cardiovascular silhouette covered by the slit.) In Stumpf's kymograms movement in each frame is read from top to bottom rather than bottom to top as in kymograms taken by the moving film method. Stumpf uses an unnecessarily long exposure time (2.4 seconds) with extra radiation of the patient. The long exposure results in three or four, sometimes five, heart cycles being recorded in each frame. The cramping makes interpretation more difficult. A minimum of one and one-half heart cycle is adequate and preferable in our opinion.

There is a great deal in this monograph to interest persons using this technique and clinical physiologists working in the cardiovascular field; it does little, however, to establish roentgenkymography as a practical method for wide applicability. Stumpf's observations on changes in the kymograms with exercise are particularly noteworthy. His identification of location of shrapnel fragments by type of movement and his studies of the "labile heart" and of movement of the left auricle in mitral valve disease are also of considerable interest.

The monograph is well printed on fine paper. Only one electrocardiogram is inverted (Fig. 32, p. 35). The very numerous photographic reproductions of roentgenkymograms (about 150 in all) are best studied with a magnifying glass.

V. A. M.

Psychosomatic Gynecology: Including Problems of Obstetrical Care. By WILLIAM S. KROGER AND S. CHARLES FREED. 503 pp., $8.00. *W. B. Saunders Co., Philadelphia, Pa.*

Into a comparatively small volume, Kroger and Freed have incorporated a phenomenal amount of obstetric, gynecologic and psychiatric data. More than this, however, their material is intelligently integrated and presented from a perspective that has been too long neglected at the post-graduate as well as the undergraduate level of medical education. Despite the difficulties encountered in a task of such magnitude, the authors have succeeded in both stimulating the imagination and challenging, without offending, the therapeutic program of every physician to whom the troubled female comes with a complaint of female trouble.

The book is conveniently divided into five parts—the first of which deals chiefly with the early influences upon personality development. Beginning biologically with a review of Sontag's important prenatal studies, the authors proceed to a discussion of the social relationships between mother and child in the post-natal period—presenting the pros and cons of breast feeding and the rooming-in plan. The section concludes with a detailed description of the psycho-analytic theory of psychosexual development, and an attempt to relate early maladjustments at each of the five stages to later functional reproductive disorders.

In part 2 the psychosomatic aspects of pregnancy are introduced with a contribution on

"natural childbirth" by Grantly Dick Read. Although still warmly and passionately written, the unreasonable—and occasionally undigestible—claims that characterized Read's earlier works are now fortunately absent. In a later chapter, the authors compare Read's program of "natural childbirth" with their own experience in the use of hypnotic technics in labor. The remaining portion of part 2 is concerned with a review of the significant psychodynamic factors in the etiology and treatment of such common obstetrical complications as hyperemesis gravidarum, pre-eclamptic toxemia, spontaneous abortion and other related disorders.

Part 3 is devoted to a discussion of the neuro-endocrine mechanisms which contribute toward the development of such functional menstrual disorders as amenorrhea, dysmenorrhea, irregular uterine bleeding, premenstrual tension and pseudocyesis. In part 4 the psychodynamic mechanisms in a heterogenous group of psychosomatic disturbances are carefully described. Among these, the problems of sterility, frigidity, dysparunia, vaginismus, obesity, pruritis, homosexuality, and the menopause receive the greatest emphasis. Part 5 concludes the book with some general remarks on diagnostic and therapeutic methods. In this, there is included some rather pertinent advice relating to pre-operative and post-operative care.

One cannot do full justice to such an ambitious undertaking as this book through a brief summary of its contents. Naturally, the book has its faults, but any criticism must be tempered with a reminder that it fills adequately a long existing professional need. A few of its weaknesses have been anticipated and acknowledged by the authors in the introductory chapter where suitable apologies appear for (1) apparent repetition, (2) questionable interpretations, and (3) the controversial and speculative nature of their material. Much of this was unavoidable due to the limitations in our present knowledge of these topics. Wherever possible, however, debatable subjects are presented fairly, with no single aspect being emphasized disproportionately, and the approach balanced by an understanding of the multi-etiologic nature of every illness.

One question is justified, perhaps, regarding the over-all serviceability of this book. Although interestingly written as a reference for the special student, for several reasons the average physician will not find it easy reading. In the first place, many will experience difficulty in accepting all of the psychoanalytic formulations that appear throughout the text. Unless applicable to practical therapeutic procedures, complex technical hypotheses tend to discourage rather than to stimulate the beginner. Finally, one has the feeling that greater discrimination in screening the bibliography (even at the risk of making for a less encyclopedic reference) would not have altered the effectiveness of this book. Little would have been lost, for example, by omitting Walser's unsupported observations on "two cases of anencephalic monsters born of neurotic women who had fantasies and dreams wherein they did not see their babies' heads."

These and other minor criticisms cannot change the value of this text as an important contribution to the growing library of psychosomatic literature. It can be recommended to physicians generally, and should be required reading for those addicted to the scalpel and hypodermic syringe.

A. J. M.

Connective Tissues. Transactions of the First Conference, April 24–25, 1950. Edited by CHARLES RAGAN. 164 pp., $3.25. *Josiah Macy, Jr. Foundation, New York.*

"If, by some magic solution, one could at once dissolve all the connective tissue of the body, all that would remain would be a mass of slimy epithelium, quivering muscle, and frustrated nerve cells." In these words a teacher of the reviewer once dramatically characterized the importance of the connective tissues in our bodies.

In an unusually informal manner, the First Conference on Connective Tissue of the Josiah Macy, Jr. Foundation re-emphasizes the fundamental role of connective tissues in both health and in disease in general. The verbatim report of informal discussions of general topics relating to connective tissue is presented in a short monograph.

The topics discussed were: Structure and Function of Normal Connective Tissue (D. Murray Angevine); Pathology of Connective Tissue, Fibrinoid Degeneration (Granville A. Bennett); Chemistry of Connective Tissue, Polysaccharides (Karl Meyer); Enzymatically Modified Ovalbumins (Gertrude E. Perlmann); Effects of ACTH and Cortisone on Connective Tissues (Charles Ragan). This list in itself reveals the broad scope of the conference.

The discussions, for the most part, are lucid, erudite, and thought provoking. However, there are too many "slow lines" or "idle words," that could well have been deleted. A summary, after each chapter, of the important points covered in the discussion would have added much, in the reviewer's opinion.

Significant errors of context are few. The reviewer believes that Dr. Murray Angevine has misunderstood the work of Gersh and Catchpole (Am. J. Anat., 1949, **85**: 457–522) on changes in the "ground substance" and "basement membrane" due to aging. Dr. Angevine says that Gersh has indicated that "as one becomes older the [connective tissue] fibers that are widely dispersed come together . . . because there is less ground substance between them." In reality, Gersh has postulated that the ground substance—a microscopically nonfibrillar, glycoprotein, intercellular material—becomes more highly polymerized and hence more dense with advancing age; thus it is less soluble with aqueous solvents. Functional variations in health and disease may cause variation in the degree of polymerization and therefore in the permeability of the ground substance (and basement membrane).

The importance of this little volume cannot be too highly stressed. It should be read by everyone interested in the connective tissues and their roles, both in the normally functioning body and in the diseased body.

J. A. A.

Einfuhrung in die Röntgenologie. By G. F. HAENISCH AND H. HOLTHUSEN. 521 pp., Ganzleinen DM 60. *Georg Thieme Verlag, Stuttgart, Germany.*

This volume is divided into two roughly equal parts, the first dealing with diagnosis and the second with therapy.

The diagnostic section begins with a discussion of the physics of X-ray diagnosis. This is followed with a good description of the equipment and general techniques employed in radiographic work.

There follows a systematic survey of normal X-ray anatomy. Diseases of the organ-systems are then covered in rather complete fashion. In many instances the discussions are more detailed than what one would expect to find in an introductory text. The accompanying X-ray reproductions are, with occasional exceptions good, but are "intermediates" in the photographic sense, the denser structures appearing darker. (Nearly all European texts reproduce radiographs in this way.) The author constantly stresses the limitations of the radiographic method. In this he has a special message of caution for radiologists, who, he feels, often attempt etiologic diagnoses where none is truly warranted by the evidence on the films.

The literary style is such that anyone with a basic knowledge of German roots can get along quite well.

The second section comprises a well conceived survey of the field of X-ray therapy, being nowhere too detailed for the general medical reader, and yet being comprehensive enough to offer a brief discussion of nearly all conditions commonly accepted as responding to Roentgen and related radiation.

This section is introduced with an excellent treatise on the physics of radiation and subatomic phenomena. The description of the effects of radiation on tissues impresses the reviewer as outstanding.

The book is recommended without reservation to those sufficiently interested in radiology to desire a basic knowledge of its methods, its applications and its limitations. As was mentioned above, a basic reading knowledge of German is necessary.

D. J. T.

BOOKS RECEIVED FOR REVIEW

Biological Antioxidants. Transactions of the Fifth Conference, November 30–December 1, 1950, New York. Edited by COSMO G. MACKENZIE. 229 pp., $3.75. *Josiah Macy, Jr. Foundation, New York.*

Blood Clotting and Allied Problems. Transactions of the Fourth Conference, January 22–23, 1951. Edited by JOSEPH E. FLYNN. 272 pp., $4.00. *Josiah Macy, Jr. Foundation, New York.*

Callander's Surgical Anatomy, 3rd edition. By BARRY J. ANSON AND WALTER G. MADDOCK. 1074 pp., $14.00. *W. B. Saunders Co., Philadelphia, Pa.*

Cerebral Mechanisms in Behavior. The Hixon Symposium. Edited by LLOYD A. JEFFRESS. 311 pp., $6.50. *John Wiley & Sons, New York.*

Das Phäochromozytom. By H. KREFELD. 93 pp., Kartoniert DM 11.70. *Georg Thieme Verlag, Stuttgart, Germany.*

Metabolic Interrelations. Transactions of the Third Conference, January 8–9, 1951. Edited by EDWARD C. REIFENSTEIN, JR. 294 pp., $4.00. *Josiah Macy, Jr. Foundation, New York.*

The Practice of Endocrinology. By RAYMOND GREENE. 389 pp., $12.50. *J. B. Lippincott Co., Philadelphia, Pa.*

Textbook of Clinical Neurology, 3rd edition. By ISRAEL S. WECHSLER. 801 pp., $9.50. *W. B. Saunders Co., Philadelphia, Pa.*

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